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Diet Soda and Sugar-Sweetened Soda Consumption in Relation to Incident Diabetes in the Northern Manhattan Study

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Abstract

Background: Artificially (diet) and sugar-sweetened (regular) soda consumption have been associated with an increased risk of diabetes, but the literature on diet soda is inconsistent and the mechanisms unclear.

Objective: We examined the relation between diet soda and regular soda consumption with the risk of incident diabetes in a longitudinal multiethnic population-based cohort.

Methods: The study population included 2019 participants (mean ± SD age: 69 ± 10 y; 64% women; 23% white, 22% black, 53% Hispanic) in the Northern Manhattan Study who were free of diabetes and stroke at baseline. Soda consumption was assessed by a food-frequency questionnaire at baseline and examined continuously and categorically (<1/mo: sugar-sweetened = 908, diet = 1615; 1/mo–6/wk: sugar-sweetened = 830, diet = 298; daily: sugar-sweetened = 281, diet = 106). Weibull regression models were used to estimate the associations between soda consumption and incident diabetes, adjusting for demographics and vascular risk factors including body mass index (BMI) and calorie consumption.

Results: During a mean ± SD follow-up of 11 ± 5 y, 368 participants developed diabetes. Sugar-sweetened soda was positively associated with incident diabetes (per soda per day HR = 1.15, 95% CI: 1.02, 1.31). The observed association between diet soda and elevated risk of diabetes was largely explained by BMI at the time of diet assessment, though the association remained strong and independent of BMI among those who were overweight or obese (daily compared to <1/mo: HR = 1.63, 95% CI: 1.04, 2.55).

Conclusions: This study supports the importance of sugar-sweetened beverage consumption in the diabetes epidemic. However, the results support previous studies suggesting that switching to artificially sweetened diet beverages may not lower the risk of diabetes, as diet soda consumption cannot be ruled out as an independent diabetes risk factor. *Curr Dev Nutr* 2018;2:nzy008.

Introduction

Frequent diet (artificially sweetened) and regular (sugar-sweetened) soda consumption have both been associated with an increased risk of cardiovascular events, though the literature on diet soda is less consistent (1, 2). In the Northern Manhattan Study (NOMAS) we observed that participants who drank diet soda daily had an increased rate of vascular events compared to those who never drank diet soda, after adjusting for vascular risk factors (2). Regular soda consumption was positively associated with the rate of vascular events among those participants free of obesity, diabetes, and metabolic syndrome at baseline. There are several pathways, including obesity and diabetes, through which regular soda, due to its high caloric content, glycemic load, and inflammatory effects (3), may increase the risk for a cardiovascular event. The pathways through which diet soda may impact the risk for a cardiovascular event are more ambiguous. The literature on the relation between diet soda consumption and obesity and weight gain is mixed and

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inconclusive (4), as for its potential relation with insulin resistance. An increased risk of diabetes among frequent consumers of diet soda has been reported in some epidemiologic studies (5, 6), but further research is needed. Whether the association between diet soda consumption and diabetes risk is causal is particularly unclear. In contrast, the increased risk of developing diabetes among frequent consumers of regular sugar-sweetened soda is more established (3, 7), but the relative effect compared to artificially sweetened diet soda is unknown.

The public health importance of understanding the relation between soda consumption and the risk of diabetes is underscored by the high prevalence of both soda consumption and diabetes in the population. The age-adjusted prevalence of sugar-sweetened beverage consumption among US adults was estimated to be 30% in 2013 (8). The 2009–2010 NHANES survey suggested that ~20% of the US population consumed diet drinks on a given day (9), and recent data suggest that the consumption of low-calorie sweeteners is increasing (10). From 2007 to 2008 the percentage of adults consuming diet beverages increased from 19% to 24% (11). It was estimated that 284 million individuals were living with diabetes worldwide in 2010, with prevalence estimates rising (12). Our goal is to examine the relation between diet and regular soda consumption with the risk of incident diabetes in the multiethnic population-based NOMAS cohort. We hypothesize that diet and regular soda consumption will be associated with an increased risk of diabetes, with a stronger association observed for regular soda consumption.

Methods

Study population

NOMAS is a prospective population-based cohort study, which recruited during 1993–2001, with the original goal of identifying the incidence of and risk factors for stroke in a multiethnic urban adult population. Northern Manhattan is a well-defined region of New York City with a race/ethnic distribution of 63% Hispanic, 20% non-Hispanic black, and 15% non-Hispanic white residents (13). Participants were selected using random-digit dialing with the following eligibility criteria: *1*) never diagnosed with stroke; *2*) >40 y of age; and *3*) resided in Northern Manhattan for ≥3 mo, in a household with a telephone. The telephone response rate was 91%, and these subjects were invited for an in-person interview and physical assessment. With an enrollment response rate of 75%, 3298 subjects were enrolled and followed with an average annual contact rate of 95%. The study was approved by the Columbia University and University of Miami Institutional Review Boards and all subjects provided written informed consent.

For this analysis we excluded participants with diabetes mellitus at baseline (n = 715), defined by the participant's self-reported diabetes, use of insulin or oral antidiabetic medication, or fasting glucose ≥126 mg/dL. We also excluded participants with missing data for soda consumption (n = 492), and those with improbable total daily kilocalories based on food-frequency responses (<500 or >4000 kcal/d, n = 90).

Baseline assessment

Baseline interviews were conducted by trained bilingual research assistants. Physical and neurologic examinations were conducted by study neurologists. Race/ethnicity was based upon self-identification through a series of questions modeled after the US census and conforming to standard definitions outlined by Directive 15 (14). Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the CDC regarding hypertension, diabetes, smoking, and cardiac conditions (15, 16). Physical activity was defined as the frequency and duration of 14 recreational activities during the 2-wk period before the interview, described previously (17). Moderate alcohol consumption was defined as >1 drink/mo but ≤2 drinks/d over the previous year. Smoking was categorized as never, former, or current (within the past year) smoking cigarettes, pipes, or cigars. Hypertension was defined as blood pressure ≥140/90 mm Hg (based on the average of 2 measurements with mercury sphygmomanometers during 1 sitting), the participant's self-reported hypertension, or antihypertensive medication use. Fasting lipid profile was measured at enrollment. Fasting blood specimens were analyzed at the Core Laboratory of the Irving Center for Clinical Research to determine glucose, HDL, and TGs. Hypercholesterolemia was defined as total cholesterol concentration of >200 mg/dL, statin use, or self-reported history of hypercholesterolemia.

Diet

At baseline, participants were administered a modified Block National Cancer Institute FFQ by trained research assistants, in English or Spanish. This FFQ is designed to measure typical dietary habits over the previous year. The FFQ contained questions regarding the average consumption of diet and regular soft drinks. The possible responses were: never or <1/mo, 1–3/mo, 1/wk, 2–4/wk, 5–6/wk, 1/d, 2–3/d, 4–5/d, and ≥6/d.

The primary exposures of interest, average diet and regular soda consumption, were examined separately as categorical variables: none (<1/mo = referent), light (1/mo–6/wk), daily (≥1/d). Diet and regular soda consumption were also examined continuously as sodas per day, assigning the middle value for each category (<1/mo = 0/d, 1–3/mo = 0.07/d, 1/wk = 0.14/d, 2–4/wk = 0.43/d, 5–6/wk = 0.79/d, 1/d = 1/d, 2–3/d = 2.5/d, 4–5/d = 4.5/d, and ≥6/d = 6.5/d). Diet and regular soda variables were examined as distinct variables and mutually adjusted in multivariable analyses as some participants drank both types of soda. We also ran analyses looking at regular and diet soda consumption combined, as overall soda consumption, by adding together the continuous measures of diet and regular soda.

A score representing level of adherence to a Mediterranean-style diet was created as a covariate, as described previously (18).

Follow-up for incident diabetes

Annual telephone follow-up was conducted for study participants to identify changes in vital status, neurologic events, cardiac symptoms, vascular risk factors, medications, and functional status. An in-person evaluation was conducted for participants who reported a neurologic or cardiovascular event, or if medical records indicated that such an event occurred. Medical records were reviewed for hospitalizations between follow-ups. Annual follow-up interviews included questions about diabetes status. Incident type 2 diabetes was defined as a positive response to ≥1 of the following questions: "Since we last contacted you, have you been newly diagnosed with diabetes or high blood sugar?" or "Do you currently take any of the following medications: insulin or oral hypoglycemics?" Changes in diabetes status between follow-up visits were

confirmed by medical record review, as described and validated previously (19, 20).

Statistical analyses

Associations between diet and regular soda consumption and vascular risk factors were examined using chi-square tests for categorical variables and ANOVA for continuous variables. The primary outcome, onset of diabetes, occurred at an unknown time point before the first self-report of diabetes at annual follow-up and after the last annual report with a negative response to all of the diabetes questions. Therefore, a model allowing for interval censored data was used to examine the relation between soda consumption and incident diabetes. HRs and 95% CIs were estimated using Weibull regression models with interval censoring failure time. Follow-up time extended from baseline evaluation to onset of self-reported diabetes, death, or the end of follow-up, whichever came first. A sequence of multivariable-adjusted models was constructed: model 1 included age, sex, and race/ethnicity in addition to both diet and regular soda consumption. Model 2 additionally included a Mediterranean-diet score, total calories, smoking, moderate-heavy physical activity, and moderate alcohol use. Model 3 additionally included BMI (in kg/m^2), hypertension, and hypercholesterolemia. A sensitivity analysis controlled for waist:hip-circumference ratio instead of BMI in model 3. Model 3 was also stratified by obesity (BMI ≥25 compared to <25). Effect modification by race/ethnicity was examined by including interaction terms with each type of soda in model 3. In each model both types of soda were examined continuously and categorically. Secondary analyses were conducted with the continuous measure of all soda consumption (diet and regular soda combined). Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Bias due to reverse causation or confounding is an important threat to validity of the analyses, particularly for diet soda consumption. In order to limit this source of bias, we ran a set of sensitivity analyses excluding the first 3 y of follow-up.

Results

In total, 2019 NOMAS participants had diet data and follow-up and were free of diabetes at baseline. Of these, 368 developed diabetes during a mean ± SD follow-up of 11 ± 5 y. **Table 1** shows the frequency of diet and regular soda consumption in the cohort and the number of incident cases observed for each category. Regular soda consumed was <1/mo by 908 participants, 1/mo–6/wk by 830 participants, and daily by 281 participants. Diet soda consumed was <1/mo by 1615 participants, 1/mo–6/wk by 298 participants, and daily by 106 participants. The study population is described in relation to the covariates in **Table 2**. Sixty-four percent were women, 23% white, 22% black, and 53% Hispanic. Diet soda drinkers were more likely to be white and have a higher BMI compared to those who did not drink diet soda, and light diet soda drinkers were more likely to report moderate alcohol use. Regular soda drinkers were slightly younger, more likely to be men, black, and have lower adherence to a Mediterranean-style diet and higher energy intake compared to those who did not drink regular soda.

TABLE 1 Frequency of diet and regular soda consumption in the study cohort overall and among the incident diabetes cases

Frequency of consumption	Diet soda, *n* (*n* with incident diabetes)	Regular soda, *n* (*n* with incident diabetes)
<1/mo	1615 (286)	908 (154)
1–3/mo	109 (21)	275 (50)
1/wk	68 (15)	170 (33)
2–4/wk	91 (16)	301 (60)
5–6/wk	30 (2)	84 (17)
1/d	66 (17)	188 (25)
2–3/d	32 (9)	72 (22)
4–5/d	7 (2)	16 (6)
≥6/d	1 (0)	5 (1)
Total	2019 (368)	2019 (368)

Table 3 shows the associations of diet and regular soda assessed continuously with incident diabetes across the sequence of multivariable adjusted models, and **Table 4** shows these associations for diet and regular soda assessed categorically. In all models with the continuous soda variable, the risk of incident diabetes increased with greater consumption of soda of any kind, and with greater consumption of regular soda specifically. The relation with regular soda was not attenuated after controlling for vascular risk factors, but did vary by BMI categories. The association was most apparent among those with normal BMI (<25) at baseline, as shown in stratified analyses presented in **Table 5**. There were no apparent differences when the cohort was stratified by the sex-specific median of waist:hip ratio, an alternative measure of obesity (data not shown). However, when regular soda consumption was examined categorically, the increased risk for light and daily consumption (compared to <1/mo) did not reach statistical significance.

Models 1 and 2 show a positive association between diet soda consumption and the rate of incident diabetes, with effect estimates stronger than those observed for regular soda. In these models, moreover, participants who consumed diet soda daily had a 1.9-fold increased rate of diabetes compared to those who consumed it <1/mo. The increased rate of diabetes among those who consumed diet soda less frequently was not significant. When we further adjusted for BMI, hypertension, and hypercholesterolemia in model 3, the associations for diet soda (continuous and categorical) were attenuated and no longer statistically significant. The attenuation was primarily due to controlling for BMI, and after adjusting for waist:hip ratio instead of BMI in model 3 the results were significant and similar to those in model 2. When we stratified model 3 by normal BMI compared to overweight or obese (Table 5), we saw that the associations were stronger among those who were overweight and obese. Among those who were overweight or obese, model 3 showed a 63% increased rate of diabetes for daily diet soda consumers. Effect modification by race/ethnicity was not observed for diet or regular soda consumption in relation to diabetes risk ($P > 0.05$).

Results from sensitivity analyses excluding the first 3 y of follow-up in models 2 and 3 are also shown in Table 3 (for continuous analyses) and Table 4 (for categorical analyses). The results remained unchanged for the association between regular soda consumption and diabetes risk. The relation for diet soda is more susceptible to bias due to reverse confounding. Overall the conclusions remained unchanged, with slight changes in effect estimates and confidence bounds. However, in model 3, daily diet soda consumption was significantly associated with an increased rate of incident diabetes when we excluded the first 3 y of follow-up.

TABLE 2 Baseline characteristics of the study population, overall and by soda consumption category

Variable	Overall cohort	Diet soda			Regular soda		
		<1/mo	1/mo–6/wk	Daily	<1/mo	1/mo–6/wk	Daily
Age,[1] y	69 ± 10[2]	69 ± 11	68 ± 10	68 ± 10	70 ± 11	68 ± 10	69 ± 10
Male sex,[1] *n* (%)	725 (36)	578 (36)	106 (36)	41 (39)	291 (32)	318 (38)	116 (41)
Race/ethnicity,[1,3] *n* (%)							
Black	449 (22)	355 (22)	70 (23)	24 (23)	153 (17)	214 (26)	82 (29)
White	456 (23)	328 (20)	93 (31)	35 (33)	276 (30)	141 (17)	39 (14)
Hispanic	1065 (53)	889 (55)	130 (44)	46 (43)	467 (51)	444 (53)	154 (55)
Other	49 (2)	43 (3)	5 (2)	1 (1)	12 (1)	31 (4)	6 (2)
Total calories[1]	1569 ± 654	1555 ± 646	1627 ± 704	1630 ± 627	1435 ± 571	1590 ± 645	1942 ± 773
Smoking, *n* (%)							
Never	971 (48)	795 (49)	127 (43)	49 (46)	443 (49)	398 (48)	130 (46)
Former	708 (35)	542 (34)	122 (41)	44 (42)	334 (37)	274 (33)	100 (36)
Current	340 (17)	278 (17)	49 (16)	13 (12)	131 (14)	158 (19)	51 (18)
Moderate-heavy physical activity, *n* (%)	200 (10)	149 (9)	38 (13)	13 (12)	101 (11)	76 (9)	23 (8)
Moderate alcohol use,[3] *n* (%)	717 (36)	565 (36)	122 (41)	30 (28)	313 (34)	305 (37)	99 (35)
BMI,[3] kg/m^2	28 ± 5	27 ± 5	29 ± 6	30 ± 7	27 ± 5	28 ± 5	28 ± 6
Waist:hip ratio	0.90 ± 0.09	0.90 ± 0.09	0.89 ± 0.10	0.90 ± 0.10	0.89 ± 0.09	0.90 ± 0.09	0.90 ± 0.09
Hypertension, *n* (%)	1431 (71)	1141 (71)	208 (70)	82 (77)	636 (70)	580 (70)	215 (77)
Hypercholesterolemia, *n* (%)	1257 (62)	1005 (62)	180 (60)	72 (68)	580 (64)	509 (61)	168 (60)
Mediterranean-style diet adherence,[1] *n* (%)							
Low (score 0–3)	589 (30)	460 (30)	88 (29)	41 (40)	244 (30)	247 (28)	98 (36)
Medium (score 4–5)	882 (44)	117 (40)	723 (45)	42 (41)	374 (46)	381 (43)	127 (47)
High (score 6–9)	512 (26)	85 (29)	407 (26)	20 (19)	199 (24)	267 (30)	46 (17)

[1] $P < 0.05$ difference for regular soda categories.
[2] Mean ± SD (all such values).
[3] $P < 0.05$ difference for diet soda categories.

Discussion

In our stroke-free multiethnic cohort we confirmed the results shown previously, that increased consumption of regular sugar-sweetened soda is a risk factor for developing type 2 diabetes. The relation for diet soda is more controversial and ambiguous. We showed an increased risk of developing diabetes among daily diet soda consumers, and the positive association between diet soda consumption and diabetes risk was even stronger than that observed for regular soda. However, that association was attenuated and just shy of statistical significance when we adjusted for BMI. This suggests 1 of 2 scenarios, or a combination: either participants with a higher BMI were at an increased risk of diabetes and more likely to be drinking diet soda, likely in an attempt to reduce caloric intake to lose weight; or diet soda consumption was increasing BMI, both before and after baseline, and thereby contributing to an increased risk of diabetes. Whereas the association for regular soda was stronger among those with normal BMI, the association for diet soda was stronger among the overweight and obese. In fact, even after controlling for BMI and the other covariates in the fully adjusted model, daily diet soda consumption was a significant predictor of incident diabetes among those participants who were overweight or obese at baseline.

One of the greatest threats to the validity of the examination of diet soda in relation to diabetes is the possibility of observed associations due to reverse causality, or confounding, if people who are prediabetic start consuming diet soda in an effort to reduce risk. To address this possibility we ran sensitivity analyses excluding the first 3 y of follow-up. We found that the associations for regular soda remained consistent,

TABLE 3 Diet and regular soda consumption, assessed continuously, in relation to incident diabetes across the sequence of multivariable-adjusted models[1]

	HR (95% CI) unit: sodas per day		
	Diet soda	Regular soda	All soda (diet + regular)
Model 1	1.16 (0.86, 1.57)	1.17 (1.04, 1.32)	1.20 (1.08, 1.32)
Model 2	1.28 (1.05, 1.56)	1.15 (1.02, 1.30)	1.18 (1.06, 1.31)
Model 3	1.11 (0.90, 1.36)	1.15 (1.02, 1.31)	1.14 (1.03, 1.27)
Model 3b	1.24 (1.02, 1.50)	1.16 (1.02, 1.31)	1.18 (1.06, 1.32)
Excluding the first 3 y of follow-up			
Model 2	1.35 (1.11, 1.65)	1.16 (1.02, 1.32)	1.20 (1.08, 1.34)
Model 3	1.16 (0.94, 1.43)	1.16 (1.02, 1.32)	1.16 (1.04, 1.30)

[1] Model 1: adjusted for age, sex, race/ethnicity. Model 2: adjusted for the variables in model 1 and for Mediterranean diet, total calories, smoking, physical activity, moderate alcohol use. Model 3: adjusted for the variables in model 2 and for BMI, hypertension, hypercholesterolemia. Model 3b: controls for waist:hip ratio rather than BMI.

TABLE 4 Diet and regular soda consumption, assessed categorically, in relation to incident diabetes across the sequence of multivariable-adjusted models[1]

	HR (95% CI) reference level: <1/mo			
	Diet soda		Regular soda	
	1/mo–6/wk	Daily	1/mo–6/wk	Daily
Model 1	1.16 (0.86, 1.57)	1.87 (1.23, 2.86)	1.06 (0.83, 1.35)	1.12 (0.81, 1.55)
Model 2	1.14 (0.84, 1.56)	1.89 (1.23, 2.92)	1.07 (0.84, 1.37)	1.12 (0.79, 1.58)
Model 3	1.05 (0.77, 1.43)	1.44 (0.93, 2.24)	1.10 (0.86, 1.40)	1.13 (0.81, 1.61)
Model 3b	1.13 (0.83, 1.56)	1.81 (1.17, 2.81)	1.06 (0.82, 1.35)	1.11 (0.78, 1.57)
Excluding the first 3 y of follow-up				
Model 2	0.99 (0.70, 1.39)	0.90 (0.64, 1.28)	1.08 (0.83, 1.40)	1.10 (0.84, 1.44)
Model 3	2.16 (1.39, 3.35)	1.63 (1.04, 2.56)	1.13 (0.79, 1.62)	1.15 (0.80, 1.66)

[1]Model 1: adjusted for age, sex, race/ethnicity. Model 2: adjusted for variables in model 1 and for Mediterranean diet, total calories, smoking, physical activity, moderate alcohol use. Model 3: adjusted for variables in model 2 and for BMI, hypertension, hypercholesterolemia. Model 3b: controls for waist:hip ratio rather than BMI.

as expected, and the associations for diet soda in fact became stronger. In these sensitivity analyses, those who consumed diet soda daily had an increased risk of developing diabetes even after adjusting for BMI and the other covariates in the fully adjusted model. Instead of refuting the observed associations for diet soda, these sensitivity analyses in fact supported the possibility that diet soda consumption may be a risk factor for incident diabetes.

One interesting and unexpected finding was the important impact of general obesity, measured by BMI, on the association between diet soda consumption and diabetes risk, in contrast to the relatively nonexistent impact of abdominal obesity, measured by waist:hip ratio. Waist:hip ratio was not associated with diet or regular soda at baseline in univariate cross-sectional analyses, in contrast to BMI which was associated with diet soda consumption. Because previous studies have shown that abdominal obesity is a more important risk factor for cardiovascular disease than general obesity (21), and abdominal obesity is the measure included in the calculation of metabolic syndrome, we predicted that waist:hip ratio would be a stronger confounder, which we did not observe. This suggests that diet soda consumption may not have a disproportionate impact on abdominal obesity, or that general obesity (BMI) is a greater predictor of people's decision to consume diet soda over regular soda as compared to abdominal obesity, or that general obesity has a stronger mediating effect on the relation between diet soda and diabetes risk than abdominal obesity, or a combination of these factors. Further research is needed to better understand the different types of adiposity and how they may differentially explain a relation between soda consumption and diabetes risk.

A meta-analysis of 17 prospective cohort studies was recently conducted to estimate the effects of sugar-sweetened beverages, artificially sweetened beverages, and fruit juice on the incidence of type 2 diabetes (22). An increase in sugar-sweetened beverages of 1 serving/d was associated with an 18% increased incidence of type 2 diabetes, and this estimate remained significant but was attenuated to 13% when the potential for mediation and confounding by adiposity was accounted for. With 54% of people in the US consuming sugar-sweetened beverages in this meta-analysis, if the effect of sugar-sweetened beverages is partly mediated by adiposity, sugar-sweetened beverage consumption was estimated to result in 2.6 million excess events of type 2 diabetes over a 10-y period in the US. For artificially sweetened beverages the incidence of type 2 diabetes was 25% greater for a 1-serving increase/d, and this estimate was attenuated to 8% after adjusting for adiposity, but remained statistically significant. The effects of substituting various beverage types for sugar-sweetened beverages on type 2 diabetes risk was examined in the European Prospective Investigation into Cancer and Nutrition-Norfolk Study. They concluded that substituting artificially sweetened (diet) beverages for sugar-sweetened ones did not reduce the incidence of type 2 diabetes, though substitution with water did result in a statistically significant decrease in risk (23).

Our results are consistent with previous studies showing that frequent consumption of regular sugar-sweetened beverages increases the risk of diabetes (24–27). However, some studies have shown an association between diet soda consumption and diabetes risk that persisted after adjustment for measures of adiposity (6, 26), whereas others have not (24, 25). For example, in the Multi-Ethnic Study of Atherosclerosis

TABLE 5 Diet and regular soda consumption in relation to incident diabetes, stratified by normal BMI vs. overweight/obese[1]

	HR (95% CI)					
			Categorical reference level: <1/mo			
	Continuous unit: sodas per day		Diet soda		Regular soda	
	Diet soda	Regular soda	1/mo–6/wk	Daily	1/mo–6/wk	Daily
Among those with BMI <25	0.39 (0.05, 3.12)	1.55 (1.10, 2.19)	1.39 (0.56, 3.43)	*	0.74 (0.37, 1.45)	1.09 (0.45, 2.61)
Among those with BMI ≥25	1.18 (0.97, 1.45)	1.09 (0.95, 1.26)	1.02 (0.73, 1.41)	1.63 (1.04, 2.55)	1.10 (0.84, 1.43)	1.09 (0.75, 1.61)

[1]BMI is in kg/m^2. Model 3: Adjusted for age, sex, race/ethnicity, Mediterranean diet, total calories, smoking, physical activity, moderate alcohol use, BMI, hypertension, hypercholesterolemia.
*Model did not converge due to limited sample size.

(MESA; aged 45–84 y, mean age 62 y, 47% men, 14% smokers, mean BMI 28), daily diet soda consumers had a 67% greater risk of developing diabetes during follow-up compared to nonconsumers (6). Adjusting for baseline measures of obesity, including BMI and waist circumference, and changes over time in these measures, attenuated their observed associations between diet soda consumption and risk of diabetes, consistent with our findings, but in MESA the associations remained statistically significant.

Though the underlying mechanisms for regular soda as a risk factor for diabetes are clear, the mechanisms through which diet soda may be causally linked to diabetes risk are currently more theoretic. In the San Antonio Longitudinal Study of Aging, diet soda intake was positively associated with abdominal obesity in a dose-dependent manner (4). However, studies on the relation between artificially sweetened beverages and weight gain have been mixed. Consumption of artificial sweeteners may increase the desire for high-glycemic and calorie-dense foods or they may interfere with physiologic processes that enable people to predict the caloric content of food based on sweet taste (28), resulting in overconsumption of calories. Direct metabolic effects of artificial sweeteners remain possible mechanisms, and impacts of artificial sweeteners on various metabolic processes, including glycemic and insulin responses, have been shown (29–31). The range of hypothesized mechanisms linking diet soda consumption and diabetes also include effects on hormones and microbiota, and potential impacts of the caramel coloring and phosphoric acid in diet sodas (22).

The most important strength of our study is the excellent follow-up rate. Loss to follow-up was <1%. Other strengths include the use of a validated and well-established FFQ representing average diet over the previous year, a population-based multiethnic cohort with a large proportion of Hispanics who have been understudied in the literature on diabetes, and comprehensive data on other risk factors for diabetes. However, there are also some methodologic limitations. Most notably, both soda consumption and diabetes were recorded based on self-report and were therefore susceptible to misclassification. However, the self-reported diabetes variable has been shown to have high reliability in NOMAS. In a previous study, all participants who reported a medical diagnosis of diabetes were shown to have the diagnosis recorded in their medical records, and the same was true for >90% of participants who reported the use of diabetes medications (19). It is possible that some participants developed diabetes during follow-up despite no self-report, but this misclassification is likely unrelated to soda consumption. In addition, residual confounding by measured and unmeasured risk factors for diabetes is an important potential source of bias in our study. We could not account for changes in adiposity or diet prior to enrollment, which may have impacted the associations observed. We also lacked data on the specific types of diet sodas consumed when our diet data were collected in 1993–2001. Different types of diet sodas and different artificial sweeteners may have different physiologic responses and potential effects on diabetes risk. This possibility should be explored further in future studies. Our results may not generalize to younger populations <40 y old.

In conclusion, in this prospective multiethnic population-based cohort, consumption of regular sugar-sweetened soda was positively associated with risk of incident diabetes, particularly among those who were normal weight. We also showed an association between consumption of diet artificially sweetened sodas and an elevated risk of incident diabetes, that was largely explained by BMI at the time of diet assessment, though the association remained strong and independent of BMI among those who were overweight or obese. This study adds to a growing literature underscoring the importance of sugar-sweetened beverage consumption in the diabetes epidemic. However, our results suggest that switching to artificially sweetened diet beverages may not be the answer, as diet soda consumption may also be an independent risk factor for diabetes.

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The authors' contributions were as follows—TR, MSVE, and RLS: conducted research; HG and YPM: analyzed data or performed statistical analysis; HG: wrote paper and had primary responsibility for final content; and all authors: designed research, and read and approved the final manuscript.

References

1. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr 2009;89(4):1037–42.
2. Gardener H, Rundek T, Markert M, Wright CB, Elkind MS, Sacco RL. Diet soft drink consumption is associated with an increased risk of vascular events in the Northern Manhattan Study. J Gen Intern Med 2012;27(9):1120–6.
3. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292(8):927–34.
4. Fowler SP, Williams K, Hazuda HP. Diet soda intake is associated with long-term increases in waist circumference in a biethnic cohort of older adults: the San Antonio Longitudinal Study of Aging. J Am Geriatr Soc 2015;63(4):708–15.
5. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. Eur J Nutr 2014;53(1):251–8.
6. Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR Jr. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2009;32(4):688–94.
7. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 2010;33(11):2477–83.
8. Park S, Xu F, Town M, Blanck HM. Prevalence of sugar-sweetened beverage intake among adults – 23 states and the District of Columbia, 2013. MMWR Morb Mortal Wkly Rep 2016;65(7):169–74.
9. Fakhouri TH, Kit BK, Ogden CL. Consumption of diet drinks in the United States, 2009–2010. NCHS Data Brief 2012;109:1–8.
10. Sylvetsky AC, Rother KI. Trends in the consumption of low-calorie sweeteners. Physiol Behav 2016;164(Pt B):446–50.
11. Sylvetsky AC, Welsh JA, Brown RJ, Vos MB. Low-calorie sweetener consumption is increasing in the United States. Am J Clin Nutr 2012;96(3):640–6.
12. Farag YM, Gaballa MR. Diabesity: an overview of a rising epidemic. Nephrol Dial Transplant 2011;26(1):28–35.
13. Sacco RL, Anand K, Lee HS, Boden-Albala B, Stabler S, Allen R, Paik MC. Homocysteine and the risk of ischemic stroke in a triethnic cohort: the NOrthern MAnhattan Study. Stroke 2004;35(10):2263–9.
14. Wallman KK, Hodgdon J. Race and ethnic standards for Federal statistics and administrative reporting. Stat Report 1977(77-110):450–4.
15. Kargman DE, Sacco RL, Boden-Albala B, Paik MC, Hauser WA, Shea S. Validity of telephone interview data for vascular disease risk factors in a racially mixed urban community: the Northern Manhattan Stroke Study. Neuroepidemiology 1999;18(4):174–84.

16. Sacco RL, Elkind M, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. The protective effect of moderate alcohol consumption on ischemic stroke. JAMA 1999;281(1):53–60.
17. Willey JZ, Moon YP, Paik MC, Boden-Albala B, Sacco RL, Elkind MS. Physical activity and risk of ischemic stroke in the Northern Manhattan Study. Neurology 2009;73(21):1774–9.
18. Gardener H, Wright CB, Gu Y, Demmer RT, Boden-Albala B, Elkind MS, Sacco RL, Scarmeas N. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. Am J Clin Nutr 2011;94(6):1458–64.
19. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, Sacco RL, Elkind MS. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke 2012;43(5):1212–17.
20. Kulick ER, Moon YP, Cheung K, Willey JZ, Sacco RL, Elkind MS. Racial-ethnic disparities in the association between risk factors and diabetes: the Northern Manhattan Study. Prev Med 2016;83:31–6.
21. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev 2012;13(3):275–86.
22. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ 2015;351:h3576.
23. O'Connor L, Imamura F, Lentjes MA, Khaw KT, Wareham NJ, Forouhi NG. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages. Diabetologia 2015;58(7):1474–83.
24. de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr 2011;93(6):1321–7.
25. InterAct Consortium, Romaguera D, Norat T, Wark PA, Vergnaud AC, Schulze MB, van Woudenbergh GJ, Drogan D, Amiano P, Molina-Montes E, et al. Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. Diabetologia 2013;56(7):1520–30.
26. Fagherazzi G, Vilier A, Saes Sartorelli D, Lajous M, Balkau B, Clavel-Chapelon F. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr 2013;97(3):517–23.
27. Malik VS, Hu FB. Sweeteners and risk of obesity and type 2 diabetes: the role of sugar-sweetened beverages. Curr Diab Rep 2012;12(2):195–203.
28. Swithers SE, Davidson TL. A role for sweet taste: calorie predictive relations in energy regulation by rats. Behav Neurosci 2008;122(1):161–73.
29. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, Williamson DA. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite 2010;55(1):37–43.
30. Pepino MY, Tiemann CD, Patterson BW, Wice BM, Klein S. Sucralose affects glycemic and hormonal responses to an oral glucose load. Diabetes Care 2013;36(9):2530–5.
31. Sylvetsky AC, Brown RJ, Blau JE, Walter M, Rother KI. Hormonal responses to non-nutritive sweeteners in water and diet soda. Nutr Metab (Lond) 2016;13:71.