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Diet Soda Intake and Risk of Incident Metabolic Syndrome and Type 2 Diabetes in the Multi-Ethnic Study of Atherosclerosis

Running Title: *Diet soda, metabolic syndrome and diabetes*

Jennifer A. Nettleton, PhD[1], Pamela L. Lutsey, PhD[2], Youfa Wang, MD, PhD[3], João A. Lima, PhD[4], Erin D. Michos, MD[4], and David R. Jacobs, Jr, PhD[2, 5]
From the [1]Division of Epidemiology, University of Texas Health Sciences Center, Houston, TX, the [2]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN; [3]Center for Human Nutrition, Department of International Health and [4]Division of Cardiology, Johns Hopkins University, Baltimore, MD; the [5]Department of Nutrition, University of Oslo, Oslo, Norway

The authors have no conflicts of interest to disclose.

Address correspondence to:
Dr. Jennifer Nettleton,
E-mail: jennifer.a.nettleton@uth.tmc.edu

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Objectives: We determined associations between diet soda consumption and risk of incident MetSyn, its components, and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis.

Research Design & Methods: Diet soda consumption was assessed by food frequency questionnaire at baseline (2000-02). Incident type 2 diabetes was identified at three follow-up exams (2002-03, 2004-05, 2005-07) as fasting glucose >126 mg/dL, self-reported type 2 diabetes, or use of diabetes medication. MetSyn (and components) were defined by National Cholesterol Education Program Adult Treatment Panel 3 criteria. Hazard ratios (HR with [95% CI]) for type 2 diabetes, Met Syn, and MetSyn components, were estimated adjusting for demographic, lifestyle, and dietary confounders.

Results: At least daily consumption of diet soda was associated with a 36% greater relative risk of incident MetSyn and a 67% greater relative risk of incident type 2 diabetes compared to non-consumption (1.36 [1.11, 1.66] for MetSyn; 1.67 [1.27, 2.20] for type 2 diabetes). Of MetSyn components, only high waist circumference (men: ≥102 cm; women: ≥88 cm) and high fasting glucose (≥100 mg/dL) were prospectively associated with diet soda consumption. Associations between diet soda consumption and type 2 diabetes were independent of baseline measures of adiposity or changes in these measures, whereas associations between diet soda and MetSyn were not independent of these factors.

Conclusions: Although these observational data cannot establish causality, consumption of diet soda at least daily was associated with significantly greater risks of select incident MetSyn components and type 2 diabetes.

Two longitudinal cohort studies have shown positive associations between diet soda consumption and incident MetSyn independent of baseline measures of adiposity (1; 2). Artificially-sweetened beverages, like diet soda, are commonly considered "benign" as they contribute no energy and few nutrients to the diet. Consequently, the previously observed diet soda-MetSyn associations are generally speculated to be the result of residual confounding by other dietary behaviors, lifestyle factors, or demographic characteristics (1; 2). Biological mechanisms possibly explaining these associations are few and largely focus on artificially-sweeteners in beverages/foods increasing the desire for (and consumption of) sugar-sweetened, energy-dense beverages/foods (3) or disrupting consumers' ability to accurately estimate energy intake and remaining energy needs (4). Thus, diet soda consumption may result in overconsumption, increased body weight, and consequent metabolic dysfunction. If true, such relations have important implications for dietary counseling, given the high frequency diet beverages are consumed by those at high risk for metabolic dysfunction (5).

Replication of previously observed diet soda-MetSyn associations in a distinct cohort would bolster their credibility and provide further insight into the nature of the relationship. Previous studies have not addressed associations between diet soda and individual MetSyn components or risk of type 2 diabetes nor have they fully addressed potential longitudinal mediators of these relationships, i.e., changes in adiposity status (body weight and or waist circumference).

Therefore, we evaluated associations between diet soda consumption and risk of incident MetSyn (and MetSyn components) as well as incident type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA), while considering the influence of multiple lifestyle confounders, including measures of baseline adiposity and changes in adiposity.

METHODS

Participants: MESA is a population-based study of 6,814 Caucasian, African-American, Hispanic, and Chinese adults, aged 45-84 years, initiated to investigate the prevalence and progression of subclinical cardiovascular disease (CVD). Self-reported race/ethnicity, other demographics, and lifestyle and clinical characteristics were collected in six field centers: Baltimore County, MD; Chicago, IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; and St. Paul, MN (6). Each examination cycle spanned 2 years, with baseline (2000-02) and three follow-up exams conducted from, 2002-03, 2004-05, and 2005-07. Institutional review board approval was obtained at all centers; all participants gave informed consent.

Type 2 diabetes: Fasting glucose was measured at each exam by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY 14650). Type 2 diabetes was defined as self-reported type 2 diabetes, fasting glucose >126 mg/dL (for mmol/L multiply by 0.0555) at any exam, or use of hypoglycemic medication. Incident cases comprise individuals without type 2 diabetes at baseline who met any one of the three criteria listed above at follow-up examinations. Consistency of the serum glucose assay over examinations was established by reanalyzing 200 samples from each of the 4 examinations over a short time period, then recalibrating the original observations.

MetSyn: MetSyn was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III definition (7) as the

presence of three or more of the following: *1*) waist ≥102 (men) or ≥88 cm (women), *2*) triglycerides ≥150 mg/dl (for mmol/L multiply by 0.0113), *3*) HDL cholesterol ≤40 (men) or ≤50 mg/dl (women) (for mmol/L multiply by 0.0259), *4*) blood pressure ≥130/85 mmHg or on antihypertensive treatment, and *5*) fasting glucose ≥100 mg/dl or on anti-hyperglycemic treatment. Participants completed standardized medical history questionnaires ascertaining medication use and previous diagnoses and provided samples for quantification of fasting insulin and lipids (8). Waist circumference was measured at the umbilicus using a standard tape measure. Body mass index (BMI) was calculated from measured height (m)/weight $(kg)^2$. Resting seated blood pressure was measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). The average of the last two measurements was used in analysis.

Dietary Intake*:* Diet was assessed at the baseline examination via food frequency questionnaire (FFQ) (8; 9). Diet soda intake was quantified from an item listing "Diet soft drinks, unsweetened mineral water" (hereafter referred to as diet soda). Sugar-sweetened soda intake was quantified from an item listing "Regular soft drinks, soda, sweetened mineral water (not diet), non-alcoholic beer" (hereafter referred to as sugar-sweetened soda). Frequency response options for these items were the following: Rare/never, 1-3/mo, 1/wk, 2-4/wk, 5-6/wk, 1/d, 2-3/d, 4-5/d, 6+/d. Participants reported serving size as small, medium, or large (weighted as intake frequency x 0.5, x 1.0, x 1.5 for small, medium, and large, respectively) (8). Intake of diet soda or regular soda was characterized as rare/never, >rare/never but <1 serving/week, >1 serving/week but <1 serving/day, and ≥1 serving/day. Participants who provided unreliable dietary information were excluded from analyses (n=630) (8).

Statistical Analyses: We used Cox proportional hazards regression to calculate hazard ratios (HR) for MetSyn and type 2 diabetes (PROC tPHREG, SAS 9.2, SAS Institute, Inc., Cary, NC). We assumed the incidence date to be the date of the exam at which type 2 diabetes or MetSyn was first identified. When estimating HR for incident type 2 diabetes, we excluded participants with prevalent type 2 diabetes (n=859) and those whose prevalent type 2 diabetes status was unknown or could not be updated over follow-up (n=328). When estimating HR for incident MetSyn, we excluded individuals with prevalent MetSyn (n=2241) and those whose MetSyn status was unknown at baseline or could not be up-dated over follow-up (n=226). When estimating HR for a given MetSyn component, we excluded participants meeting the criteria for that component at baseline. Sample sizes for these analyses are shown in the results.

Model 1 adjusted for baseline age, sex, race/ethnicity, examination site, and energy intake. Model 2 added additional possible socioeconomic or lifestyle confounders: attained education (<, =, >high school), time spent in inactive and active pursuits during leisure (MET-min/wk), smoking status (current/former/never smoker), pack years, and regular dietary supplement use (≥weekly use vs. non-weekly use). We also explored the impact of adjustment for various dietary factors (specifically, those associated with both diet soda consumption and type 2 diabetes and/or MetSyn in ours or previous studies), such as food intakes (servings/day of whole grain bread/rice/cereal/pasta, nuts/seeds, fruit, vegetables, white potatoes, refined grain bread/rice/cereal/pasta, salty snacks, desserts, red meat, processed meat, high-fat dairy, low-fat dairy, sugar-sweetened soda, coffee) or nutrient intakes (fiber, calcium, phosphorus, potassium, magnesium, sodium). Finally, to assess the contribution of adiposity, we

adjusted for 1) baseline waist circumference (continuous, in cm), baseline BMI (continuous), or both (single model), 2) change in waist circumference or body weight [most recent measurement – baseline measurement], and 3) stratified by BMI (<25 and ≥25 kg/m^2).

HR and 95% confidence intervals are presented relative to the lowest consumption category; we considered confidence intervals excluding 1.00 statistically significant.

RESULTS

Approximately 14% of participants consumed ≥1 serving of diet soda daily (19.4% of Whites, 8.6% of Blacks, 11.9% of Hispanics and 5.4% of Chinese), whereas 59% of participants reported never consuming diet soda. Fourteen percent consumed ≥1 serving of sugar-sweetened soda daily (10.7% of Whites, 20.7% of Blacks, 17.7% of Hispanics and 3.4% of Chinese), whereas 45% never consumed sugar-sweetened soda. Twenty-four percent did not consume either beverage; only 2% reported consuming ≥1 serving of both at least daily. Over follow-up, 871 cases of incident MetSyn (22.5%) and 413 cases of incident type 2 diabetes (8.2%) were identified. Demographic and lifestyle characteristics are shown in Table 1.

Diet Soda and Risk of MetSyn & Type 2 Diabetes: Compared to non-consumers, risk of MetSyn was 36% greater in those consuming ≥1 serving of diet soda daily after adjustment for demographic characteristics and energy intake (model 2, Table 2). Relative risk estimates were little changed after additional adjustment other dietary factors (foods or nutrients, *data not shown*). However, with adjustment for baseline measures of adiposity (waist circumference and/or BMI), the association was no longer significant (Table 2). Similarly, the association was strongly attenuated when adjusted for change in waist circumference or change in body weight between baseline and exam 4 (*data not shown*).

If we excluded from our analyses participants with any MetSyn component at baseline (leaving a much sampler of 1078 participants and 46 incident MetSyn cases), the HR comparing extreme diet soda consumption categories was greater (1.54 [0.65, 3.65], model 2) but not statistically significant.

Daily consumers of diet soda had 67% elevated risk of type 2 diabetes compared to non-consumers when adjusted for demographics and lifestyle factors, (model 2, Table 2). Adjustment for other dietary factors did not markedly change risk estimates (*data not shown*). When adjusted for baseline differences in waist circumference and/or BMI, HR for type 2 diabetes were slightly attenuated but remained statistically significant (Table 2). The association also remained statistically significant when adjusted for change in waist circumference (1.08 [0.75, 1.57]; 1.45 [1.12, 1.89]; 1.69 [1.28, 2.22] across increasing diet soda consumption categories compared to non-consumption, respectively). Results were similar when adjusted for change in body weight (*data not shown*).

When stratified by BMI (<25 versus ≥25 kg/m^2), HR were similar in both strata for both MetSyn and type 2 diabetes, although there were few incident cases and much larger confidence intervals in the BMI <25 strata (HR [95% CI] comparing extreme intake categories for MetSyn = 2.22 [1.10, 4.51] in BMI <25 and 1.48 [1.07, 2.05] in BMI ≥25; for type 2 diabetes = 1.94 [0.87, 4.35] in BMI <25 and 1.54 [1.15, 2.07] in BMI ≥25).

Sugar-sweetened Soda and Risk of MetSyn & Type 2 Diabetes: Although our primary analyses focused on diet soda intake, we also estimated corresponding risks for MetSyn and type 2 diabetes according to sugar-sweetened soda. Data showed no significant associations between sugar-

sweetened soda consumption and risk of either MetSyn or Type 2 Diabetes (*data not shown*).

If risk estimates for type 2 diabetes across diet soda categories were calculated in only the participants who did not consume sugar-sweetened soda (*n=2,245*), the association with diet soda consumption remained significant, though confidence intervals were wide (1.43 [0.79, 2.61]; 1.76 [1.18, 2.63]; 2.23 [1.49, 3.34], across increasing diet soda consumption categories compared to non-consumption, respectively). This was also true for MetSyn (1.63 [1.13, 2.36]; 1.36 [1.02, 1.81]; 1.81 [1.36, 2.42] across increasing diet soda consumption categories compared to non-consumption, respectively, *n=1,773*).

MetSyn Components: Compared to non-consumers, persons consuming ≥1 daily serving of diet soda had a significantly greater risk of developing high waist circumference (≥102 cm if male; ≥88 cm if female) or high fasting glucose (≥100 mg/dL) during follow-up (1.59 [1.23, 2.07] and 1.28 [1.08, 1.52] for high waist and high glucose, respectively, Table 3). Diet soda consumption was not associated with the development of other metabolic syndrome components (Table 3). As an alternative approach to address the same question, we also evaluated the amount of attenuation that occurred when MetSyn HR were adjusted for baseline measures of individual metabolic syndrome components. Similarly, the largest amount of attenuation occurred when HR for incident MetSyn were adjusted for baseline waist circumference or baseline fasting glucose concentration (comparing persons consuming ≥1 serving of diet soda versus non consumers: 1.18 [0.96, 1.44] adjusted for waist circumference; 1.23 [1.00, 1.51] adjusted for glucose; 1.37 [1.12, 1.68] adjusted for HDL-cholesterol; 1.39 [1.14, 1.70] adjusted for triglycerides; 1.29 [1.06, 1.58] adjusted for systolic and diastolic blood pressure).

Interactions: There were no significant interactions between diet soda or sugar-sweetened soda and age, sex, BMI, or waist circumference with respect to risk of MetSyn, MetSyn components, or type 2 diabetes. Results were also similar across race/ethnic strata. Furthermore, if Chinese were excluded from analyses (a group in which alternative MetSyn criteria have been suggested), results were quite similar, i.e., greater diet soda intake remained associated with greater risk of type 2 diabetes and metabolic syndrome (*data not shown*).

DISCUSSION

In MESA, diet soda consumption was positively associated with both incident MetSyn and type 2 diabetes. Associations between diet soda and risk of type 2 diabetes were of greater magnitude than the associations observed between diet soda and MetSyn. Consistent with these findings, diet soda was associated with developing high fasting glucose and high waist circumference during follow-up but not with other MetSyn components, suggesting that in this analysis, MetSyn associations were driven more by a pre-diabetic condition than the "syndrome" *per se*. The frequency of diet beverage consumption in the general population and the even greater reported consumption of diet beverages in persons at high risk for these conditions make dissemination of these findings to a wider audience imperative.

Despite accumulating evidence of the existence of these associations (1; 2), we are cautious not to conclude causality between diet soda and the diabetic or pre-diabetic condition. The possibility of confounding by other dietary and lifestyle/behavioral factors cannot be excluded from these observational studies. Three pose three questions when interpreting our results—two that are predicated on an assumption of causality, and one that is not dependent on a causal interpretation of these findings.

Is the relation between diet soda and metabolic disease mediated through changes in body weight or composition? An association between diet soda consumption and subsequent weight gain is plausible. First, it has been hypothesized that artificial sweeteners may increase hedonistic desires for sweetness and more energy dense foods (10-12). Second, over-consumption of other foods/beverages may also occur in conjunction with diet beverage consumption due to overestimation of the number of calories saved by substituting diet beverages for sugar-sweetened beverages (4). Third, the association between diet beverages and weight gain may be biased by early awareness of energy imbalance, i.e., diet beverage consumption may serve as a proxy for early (failed) attempts at weight maintenance. Nevertheless, empirical data have not universally supported these hypotheses. While data from one observational study showed that women who consumed >5.8 g saccharin daily gained slightly more weight than non-consumers over two years (13), experimental data show participants randomized to dietary regimens that include artificially sweetened foods and beverages do not gain more weight or consume more energy compared to those randomized to sugar-sweetened food/beverage regimens (14-22). However, the ideal design, one that is randomized and long-term, is notably lacking. In the current study, we found that the associations between diet beverage consumption and risk of type 2 diabetes were attenuated, but remained significant, when adjusted for baseline BMI or waist circumference or changes in body weight or waist circumference across exams. Therefore, our data do not indicate that change in body weight or fat distribution mediates the association between diet beverage consumption and *risk of type 2 diabetes*. However, associations between diet soda and ***MetSyn*** were strongly attenuated when adjusted for these measures of adiposity. Consistent with these data, only the MetSyn components high waist circumference and high fasting glucose were associated with prospectively reported diet soda consumption. These results indicate that associations between diet soda and our outcomes are largely mediated by changes in adiposity and fasting glucose—pre-diabetic or diabetic conditions and not the totality of the metabolic syndrome.

Could artificial sweetener (the constituent unique from sugar-sweetened soda) adversely affect biological processes related to insulin resistance, glucose regulation, and adiposity? Over the life of the MESA cohort, industry has utilized several artificial sweeteners for sweetening diet beverages. The sweeteners most commonly used in diet beverages have also changed from the initiation of MESA to the most recent examination. These dynamics make it difficult to attribute our findings to biological effects of a particular artificial sweetener. Mechanistic studies in randomized, controlled settings addressing how artificial sweeteners consumed from diet beverages impact early markers of metabolic dysfunction are lacking (especially considering true-to-life exposure from multiple sweeteners). Data like ours, and those that preceded ours (1; 2), suggest such research is warranted. Current literature provides data on single sweeteners only—mostly aspartame (12; 14; 16; 17; 19-24), with few using saccharin (11; 16), and none using sucralose, which was more recently introduced to the beverage market. Only one study used a combination of artificial sweeteners (but did not include sucralose) (15), and no studies were long term nor did they include measures of glycemic control or insulin sensitivity.

Is diet soda a marker for an unhealthy lifestyle and/or dietary pattern that collectively leads to metabolic dysfunction? It is known that differences in

consumption of a particular food are paralleled by differences in consumption of other foods. In the current study, dietary patterns of diet beverage consumers and non-consumers were different in several respects (i.e., regular diet beverage consumers ate more whole grains, fruit, low-fat dairy, desserts, and coffee but less high-fat dairy, processed meat, refined grains, and sugar-sweetened soda). These differences are consistent with dietary patterns that have been independently associated with lower risk of MetSyn or type 2 diabetes (1). Analogously, persons choosing to consume diet soda likely follow other healthy behaviors that influence MetSyn and type 2 diabetes risk. These dietary and lifestyle factors are all potential confounders that may be difficult to accurately characterize in epidemiological studies such as ours. However, failure to adjust fully for these protective factors would mask a positive association between diet soda and metabolic dysfunction (i.e., all are positive confounders).

Limitations of our estimation of diet soda or artificial sweetener exposure should be mentioned. Our FFQ ascertained diet soda consumption from a question that combined unsweetened mineral water and diet soda. However, we suspect that the true association between diet soda and outcomes would likely be stronger than observed associations due to dilution by the inclusion of unsweetened mineral water. Artificial sweeteners are found in many types of purchased foods and are commonly added by the individual to other beverages (e.g., coffee). Therefore, random misclassification of artificial sweetener exposure may exist, although diet soda consumers may also be more likely to consume other artificially sweetened foods.

CONCLUSIONS

Daily diet soda consumption was associated with significantly greater risks of two MetSyn components (incident high waist circumference and fasting glucose) and type 2 diabetes in this large, multi-ethnic cohort. These results corroborate findings from the ARIC and Framingham studies and show stronger adverse associations exist between diet soda and type 2 diabetes. Diet soda consumption, either independently or in conjunction with other dietary and lifestyle behaviors, may lead to weight gain, impaired glucose control, and eventual diabetes.

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Table 1. Characteristics of 5,011 participants free of prevalent type 2 diabetes according to diet soda consumption categories in the Multi-Ethnic Study of Atherosclerosis (MESA)[1]

	Rare or Never	>rare/never but <1 serving per week	≥1 serving per week – < 1 serving per day	≥1 serving per day	*P*[2]
n	2,961	455	914	681	
Median diet soda intake (serving/d)	0.0	0.1	0.4	2.5	
Sex (% male)	48.9	43.7	43.7	48.5	0.11
Age (y)	62.5 ± 0.2	61.2 ± 0.5	61.5 ± 0.3	58.9 ± 0.4	<0.001
Race/Ethnicity					<0.001
% White	34.0	46.6	58.6	62.11	
% African-American	27.0	23.7	15.4	17.8	
% Hispanic	22.7	18.0	21.1	15.3	
% Chinese	16.3	11.7	4.8	4.9	
High school degree (%)	80.3	91.2	92.5	88.5	<0.001
Active leisure (MET-min/wk)	2357 ± 56	2762 ± 143	2746 ± 101	2670 ± 117	<0.001
Inactive leisure (MET-min/wk)	1665 ± 21	1692 ± 52	1744 ± 37	1628 ± 43	0.73
Smoking (% current)	15.6	10.8	13.3	12.0	0.006
Cigarette pack years	11.5 ± 0.4	8.4 ± 1.0	10.1 ± 0.7	12.3 ± 0.9	0.87
Weekly supplement use (% current)	58.5	54.5	58.9	57.9	0.42
Fasting insulin (mg/dL)[3]	44 ± 0.7	44 ± 1.4	43 ± 0.7	45 ± 1.4	0.80
Fasting glucose (mg/dL)[3]	89.9 ± 0.2	88.7 ± 0.5	89.1 ± 0.3	89.2 ± 0.4	0.03
BMI (kg/m^2)	27.3 ± 0.1	28.3 ± 0.2	28.5 ± 0.2	29.3 ± 0.2	<0.001
Waist circumference (cm)	95.6 ± 0.3	97.2 ± 0.6	98.3 ± 0.5	100.6 ± 0.5	<0.001
Dietary Intake [4]					
Energy (kcal/d)[3]	1673 ± 14	1608 ± 36	1631 ± 25	1871 ± 29	<0.001
Protein (g/d)	65.5 ± 0.3	69.2 ± 0.7	68.3 ± 0.5	68.0 ± 0.6	<0.001
Total fat (g/d)	65.4 ± 0.2	63.5 ± 0.6	64.0 ± 0.4	63.4 ± 0.5	<0.001
Saturated fat (g/d)	20.7 ± 0.1	20.3 ± 0.3	20.5 ± 0.2	20.3 ± 0.2	0.11
Monounsaturated fat (g/d)	23.9 ± 0.1	23.1 ± 0.3	23.5 ± 0.2	23.2 ± 0.2	0.001
Polyunsaturated fat (g/d)	14.9 ± 0.1	14.0 ± 0.2	13.9 ± 0.2	13.9 ± 0.2	<0.001
Trans fat (g/d)	3.3 ± 0.03	3.3 ± 0.1	3.5 ± 0.05	3.4 ± 0.1	0.002
Carbohydrate (g/d)	210 ± 0.7	209 ± 2	207 ± 1	207 ± 1	0.007
Fiber	17.6 ± 0.1	18.7 ± 0.3	18.2 ± 0.2	17.8 ± 0.2	0.07
Calcium (mg/d)	746 ± 7	799 ± 18	794 ± 13	769 ± 15	0.006
Potassium (mg/d)	2645 ± 12	2813 ± 31	2789 ± 22	2694 ± 26	<0.001
Magnesium (mg/d)	258 ± 1	273 ± 3	274 ± 2	269 ± 35	<0.001
Phosphorus (mg/d)	1057 ± 5	1112 ± 13	1121 ± 9	1143 ± 11	<0.001
Sodium (mg/d)	2345 ± 11	2393 ± 28	2408 ± 20	2431 ± 23	<0.001
Whole grains (serving/d)	0.56 ± 0.01	0.66 ± 0.03	0.66 ± 0.02	0.62 ± 0.02	<0.001
Nuts/seeds	0.28 ± 0.01	0.29 ± 0.02	0.31 ± 0.01	0.29 ± 0.02	0.12
Fruit	1.8 ± 0.03	2.0 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	0.04
Vegetables	2.3 ± 0.02	2.4 ± 0.1	2.3 ± 0.04	2.3 ± 0.1	0.57
White potatoes	0.20 ± 0.004	0.18 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.66
White bread, rice, pasta, cereal	1.3 ± 0.01	1.2 ± 0.04	1.2 ± 0.03	1.2 ± 0.03	<0.001
Salty snacks	0.21 ± 0.01	0.22 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.05
Desserts	0.31 ± 0.01	0.29 ± 0.02	0.34 ± 0.01	0.36 ± 0.02	0.006
Low-fat dairy	0.71 ± 0.02	0.91 ± 0.05	0.89 ± 0.04	0.81 ± 0.04	<0.001
High-fat dairy	0.53 ± 0.01	0.50 ± 0.03	0.46 ± 0.02	0.47 ± 0.02	0.001
Red meat	0.38 ± 0.01	0.39 ± 0.01	0.38 ± 0.01	0.37 ± 0.01	0.33
Processed meat	0.18 ± 0.004	0.15 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.004
Non-diet soda	0.45 ± 0.02	0.31 ± 0.04	0.28 ± 0.03	0.39 ± 0.03	<0.001
Coffee	1.1 ± 0.03	1.2 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	<0.001

[1]Values represent means ± SE or percentages. Characteristics of participants free of prevalent MetSyn (n = 3878) across categories of diet soda consumption were similar.

[2]*P* for linear trend calculated with the categorical variable modeled continuously.
[3]To convert insulin from md/dL to mmol/L, multiply by 6.945. To convert glucose from mg/dL to mmol/L multiply by 0.0555.
[4]With the exception of energy intake, all dietary variables are adjusted for kcal/d. To convert kcal to kJ, multiply by 4.1868.

Table 2. Risk (HR [95% confidence intervals]) of incident MetSyn (n =3,878) and Type 2 Diabetes (n =5,011) according to diet soda consumption categories in participants from the Multi-Ethnic Study of Atherosclerosis

MetSyn				
Rare or Never	**>rare/never but <1 serving per week**	**≥1 serving per week – < 1 serving per day**	**≥1 serving per day**	*P* trend[5]
n = 2,288	*n = 367*	*n = 722*	*n = 501*	
478 cases	95 cases	169 cases	129 cases	
1.00 [1]	1.34 (1.07, 1.67)	1.20 (1.00, 1.43)	1.31 (1.07, 1.60)	0.003
1.00 [2]	1.42 (1.14, 1.78)	1.28 (1.06, 1.53)	1.36 (1.11, 1.66)	<0.001
1.00 [3]	1.31 (1.05, 1.64)	1.13 (0.94, 1.37)	1.18 (0.96, 1.44)	0.06
1.00 [4]	1.30 (1.04, 1.62)	1.15 (0.95, 1.38)	1.17 (0.96, 1.44)	0.06
Type 2 Diabetes				
Rare or Never	**>rare/never but <1 serving per week**	**≥1 serving per week – < 1 serving per day**	**≥1 serving per day**	*P* trend[5]
n = 2,961	*n = 455*	*n = 914*	*n = 681*	
221 cases	33 cases	84 cases	75 cases	
1.00 [1]	1.06 (0.73, 1.52)	1.39 (1.07, 1.80)	1.63 (1.24, 2.13)	< 0.001
1.00 [2]	1.10 (0.76, 1.59)	1.46 (1.12, 1.89)	1.67 (1.27, 2.20)	< 0.001
1.00 [3]	1.00 (0.69, 1.45)	1.23 (0.94, 1.60)	1.40 (1.06, 1.84)	0.01
1.00 [4]	0.98 (0.68, 1.42)	1.25 (0.96, 1.62)	1.38 (1.04, 1.82)	0.01

[1] HR (95% CI), Model 1: adjusted for study site, age, sex, race/ethnicity, and energy intake
[2] HR (95% CI), Model 2: adjusted for the variables in model 1 above + education, physical activity, smoking status, pack years, and ≥ weekly supplement use
[3] HR (95% CI), adjusted for the variables in model 2 above + waist circumference (cm)
[4] HR (95% CI), adjusted for the variables in model 2 above + waist circumference (cm) and BMI (kg/m^2)
[5] *P* for trend with categorical variable modeled continuously.

Table 3. Risk (HR [95% confidence intervals]) of developing MetSyn Components according to diet soda intake categories in participants from the Multi-Ethnic Study of Atherosclerosis

Rare or Never	>rare/never but <1 serving per week	≥1 serving per week – < 1 serving per day	≥1 serving per day
Blood Pressure[1]			
n = 1990	*n = 322*	*n = 602*	*n = 449*
512 cases	*74* cases	*144* cases	*113* cases
1.00 (*model 2*)[2]	1.07 (0.83, 1.37)	1.11 (0.91, 1.34)	1.17 (0.95, 1.45)
Waist Circumference[1]			
n = 1544	*n = 208*	*n = 399*	*n = 277*
282 cases	*44* cases	*93* cases	*81* cases
1.00 (*model 2*)[2]	1.13 (0.82, 1.57)	1.22 (0.95, 1.55)	***1.59 (1.23, 2.07)***
HDL-C[1]			
n = 1881	*n = 306*	*n = 609*	*n = 434*
604 cases	*97* cases	*173* cases	*127* cases
1.00 (*model 2*)[2]	1.12 (0.88, 1.44)	0.96 (0.78, 1.17)	1.05 (0.84, 1.30)
Triglycerides[1]			
n = 2143	*n = 344*	*n = 666*	*n = 476*
499 cases	*78* cases	*156* cases	*115* cases
1.00 (*model 2*)[2]	1.05 (0.82, 1.33)	1.10 (0.91, 1.33)	1.04 (0.84, 1.28)
Fasting Glucose[1]			
n = 2453	*n = 400*	*n = 793*	*n = 584*
664 cases	*97* cases	*215* cases	*177* cases
1.00 (*model 2*)[2]	0.97 (0.78, 1.21)	1.13 (0.96, 1.32)	***1.28 (1.08, 1.52)***

[1] MetSyn components defined as follows: High Blood Pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 or taking antihypertensive mediation; High Waist Circumference: ≥102 cm if male or ≥88 cm if female; Low HDL-C: <40 mg/dL if male or <50 mg/dL if female; High Triglycerides: ≥150 mg/dL; High fasting glucose: ≥100 mg/dL. To convert HDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113; to convert glucose to mmol/L, multiply by 0.0555.

[2] HR (95% CI) (model 2) adjusted for study site, age, sex, race/ethnicity, energy intake education, physical activity, smoking status, pack years, and ≥ weekly supplement use.