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

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OBJECTIVE — We determined associations between diet soda consumption and risk of incident metabolic syndrome, its components, and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis.

RESEARCH DESIGN AND METHODS — Diet soda consumption was assessed by food frequency questionnaire at baseline (2000–2002). Incident type 2 diabetes was identified at three follow-up examinations (2002–2003, 2004–2005, and 2005–2007) as fasting glucose >126 mg/dl, self-reported type 2 diabetes, or use of diabetes medication. Metabolic syndrome (and components) was defined by National Cholesterol Education Program Adult Treatment Panel III criteria. Hazard ratios (HRs) with 95% CI for type 2 diabetes, metabolic syndrome, and metabolic syndrome 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 metabolic syndrome and a 67% greater relative risk of incident type 2 diabetes compared with nonconsumption (HR 1.36 [95% CI 1.11–1.66] for metabolic syndrome and 1.67 [1.27–2.20] for type 2 diabetes). Of metabolic syndrome components, only high waist circumference (men ≥102 cm and 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 metabolic syndrome 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 metabolic syndrome components and type 2 diabetes.

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Two longitudinal cohort studies have shown positive associations between diet soda consumption and incident metabolic syndrome independent of baseline measures of adiposity (1,2). Artificially sweetened beverages, such as diet soda, are commonly considered "benign" because they contribute no energy and few nutrients to the diet. Consequently, the previously observed diet soda–metabolic syndrome 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 artificial 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 of diet beverage consumption by those at high risk for metabolic dysfunction (5).

Replication of previously observed diet soda–metabolic syndrome 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 metabolic syndrome 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 metabolic syndrome (and metabolic syndrome 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.

RESEARCH DESIGN AND METHODS

— 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:

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Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; New York, New York; Los Angeles County, California; and St. Paul, Minnesota (6). Each examination cycle spanned 2 years, with baseline (2000–2002) and three follow-up examinations conducted from 2002–2003, 2004–2005, and 2005–2007. Institutional review board approval was obtained at all centers; all participants gave informed consent.

Type 2 diabetes

Fasting glucose was measured at each examination by rate reflectance spectrophotometry using thin-film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY). Type 2 diabetes was defined as self-reported type 2 diabetes, fasting glucose >126 mg/dl (for millimoles per liter, multiply by 0.0555) at any examination, 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 four examinations over a short time period and then recalibrating the original observations.

Metabolic syndrome

Metabolic syndrome 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 millimoles per liter, multiply by 0.0113), *3*) HDL cholesterol ≤40 (men) or ≤50 mg/dl (women) (for millimoles per liter, multiply by 0.0259), *4*) blood pressure ≥130/85 mmHg or antihypertensive treatment, and *5*) fasting glucose ≥100 mg/dl or antihyperglycemic 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. BMI was calculated from measured weight in kilograms divided by the square of height in meters. 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 a food frequency questionnaire (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), nonalcoholic beer" (hereafter referred to as sugar-sweetened soda). Frequency response options for these items were the following: rare/never, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, or 6+/day. Participants reported serving size as small, medium, or large (weighted as intake frequency × 0.5, × 1.0, and × 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 (HRs) for metabolic syndrome and type 2 diabetes (PROC tPHREG in SAS 9.2; SAS Institute, Cary, NC). We assumed the incidence date to be the date of the examination at which type 2 diabetes or metabolic syndrome 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 metabolic syndrome, we excluded individuals with prevalent metabolic syndrome (n = 2,241) and those whose metabolic syndrome status was unknown at baseline or could not be updated over follow-up (n = 226). When estimating HR for a given metabolic syndrome component, we excluded participants meeting the criteria for that component at baseline. Sample sizes for these analyses are shown in 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 (less than, equal to, or more than high school), time spent in inactive and active pursuits during leisure (MET-minutes per week), smoking status (current, former, or never smoker), pack-years, and regular dietary supplement use (weekly use or more versus nonweekly 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 metabolic syndrome in ours or previous studies), such as food intakes (servings per 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 products, low-fat dairy products, sugar-sweetened soda, and coffee) or nutrient intakes (fiber, calcium, phosphorus, potassium, magnesium, and sodium). Finally, to assess the contribution of adiposity, we adjusted for *1*) baseline waist circumference (continuous, in centimeters), baseline BMI (continuous), or both (single model); *2*) change in waist circumference or body weight (most recent measurement − baseline measurement); and *3*) stratification by BMI (<25 and ≥25 kg/m^2).

HRs and 95% CIs are presented relative to the lowest consumption category. We considered CIs 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 metabolic syndrome (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 metabolic syndrome and type 2 diabetes

Compared with nonconsumers, the risk of metabolic syndrome was 36% greater in those consuming ≥1 serving of diet

Table 1—*Characteristics of 5,011 participants free of prevalent type 2 diabetes according to diet soda consumption categories in MESA*

	Rare or never	> rare/never but <1 serving per week	≥1 serving/week to <1 serving/day	≥1 serving/day	*P**
n	2,961	455	914	681	
Median diet soda intake (serving/day)	0.0	0.1	0.4	2.5	
Sex (% male)	48.9	43.7	43.7	48.5	0.11
Age (years)	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/week)	2,357 ± 56	2,762 ± 143	2,746 ± 101	2,670 ± 117	<0.001
Inactive leisure (MET-min/week)	1,665 ± 21	1,692 ± 52	1,744 ± 37	1,628 ± 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)	44 ± 0.7	44 ± 1.4	43 ± 0.7	45 ± 1.4	0.80
Fasting glucose (mg/dl)	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†					
Energy (kcal/day)	1,673 ± 14	1,608 ± 36	1,631 ± 25	1,871 ± 29	<0.001
Protein (g/day)	65.5 ± 0.3	69.2 ± 0.7	68.3 ± 0.5	68.0 ± 0.6	<0.001
Total fat (g/day)	65.4 ± 0.2	63.5 ± 0.6	64.0 ± 0.4	63.4 ± 0.5	<0.001
Saturated fat (g/day)	20.7 ± 0.1	20.3 ± 0.3	20.5 ± 0.2	20.3 ± 0.2	0.11
Monounsaturated fat (g/day)	23.9 ± 0.1	23.1 ± 0.3	23.5 ± 0.2	23.2 ± 0.2	0.001
Polyunsaturated fat (g/day)	14.9 ± 0.1	14.0 ± 0.2	13.9 ± 0.2	13.9 ± 0.2	<0.001
Trans fat (g/day)	3.3 ± 0.03	3.3 ± 0.1	3.5 ± 0.05	3.4 ± 0.1	0.002
Carbohydrate (g/day)	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/day)	746 ± 7	799 ± 18	794 ± 13	769 ± 15	0.006
Potassium (mg/day)	2,645 ± 12	2,813 ± 31	2,789 ± 22	2,694 ± 26	<0.001
Magnesium (mg/day)	258 ± 1	273 ± 3	274 ± 2	269 ± 35	<0.001
Phosphorus (mg/day)	1,057 ± 5	1,112 ± 13	1,121 ± 9	1,143 ± 11	<0.001
Sodium (mg/day)	2,345 ± 11	2,393 ± 28	2,408 ± 20	2,431 ± 23	<0.001
Whole grains (servings/day)	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 products	0.71 ± 0.02	0.91 ± 0.05	0.89 ± 0.04	0.81 ± 0.04	<0.001
High-fat dairy products	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
Nondiet 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

Data are means ± SE or %. Characteristics of participants free of prevalent metabolic syndrome (n = 3,878) across categories of diet soda consumption were similar. *P for linear trend calculated with the categorical variable modeled continuously. †With the exception of energy intake, all dietary variables are adjusted for kilocalories per day.

soda daily after adjustment for demographic characteristics and energy intake (model 2, Table 2). Relative risk estimates changed little after additional adjustment for 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 examination 4 (data not shown).

Table 2—*Risk of incident metabolic syndrome and type 2 diabetes according to diet soda consumption categories in participants from MESA*

	Rare or never	> rare/never but <1 serving/week	≥1 serving/week to <1 serving/day	≥1 serving/day	P_{trend}*
Metabolic syndrome					
n	2,288	367	722	501	
Cases	478	95	169	129	
HR (95% CI)	1.00†	1.34 (1.07–1.67)	1.20 (1.00–1.43)	1.31 (1.07–1.60)	0.003
	1.00‡	1.42 (1.14–1.78)	1.28 (1.06–1.53)	1.36 (1.11–1.66)	<0.001
	1.00§	1.31 (1.05–1.64)	1.13 (0.94–1.37)	1.18 (0.96–1.44)	0.06
	1.00‖	1.30 (1.04–1.62)	1.15 (0.95–1.38)	1.17 (0.96–1.44)	0.06
Type 2 diabetes					
n	2,961	455	914	681	
Cases	221	33	84	75	
HR (95% CI)	1.00†	1.06 (0.73–1.52)	1.39 (1.07–1.80)	1.63 (1.24–2.13)	<0.001
	1.00‡	1.10 (0.76–1.59)	1.46 (1.12–1.89)	1.67 (1.27–2.20)	<0.001
	1.00§	1.00 (0.69–1.45)	1.23 (0.94–1.60)	1.40 (1.06–1.84)	0.01
	1.00‖	0.98 (0.68–1.42)	1.25 (0.96–1.62)	1.38 (1.04–1.82)	0.01

n = 5,011. *P_{trend} with categorical variable modeled continuously. †Model 1 adjusted for study site, age, sex, race/ethnicity, and energy intake. ‡Model 2 adjusted for the variables in model 1 above plus education, physical activity, smoking status, pack-years, and weekly or more supplement use. §Adjusted for the variables in model 2 above + waist circumference (centimeters). ‖Adjusted for the variables in model 2 above + waist circumference (centimeters) and BMI (weight in kilograms divided by the square of height in meters).

If we excluded from our analyses participants with any metabolic syndrome component at baseline (leaving a much smaller sample of 1,078 participants and 46 incident cases of metabolic syndrome), the HR comparing extreme diet soda consumption categories was greater (1.54 [95% CI 0.65–3.65], model 2) but not statistically significant.

Daily consumers of diet soda had a 67% elevated risk of type 2 diabetes compared with nonconsumers with adjustment for demographics and lifestyle factors (model 2, Table 2). Adjustment for other dietary factors did not markedly change risk estimates (data not shown). With adjustment for baseline differences in waist circumference and/or BMI, HRs for type 2 diabetes were slightly attenuated but remained statistically significant (Table 2). The association also remained statistically significant with adjustment for change in waist circumference (HR 1.08 [95% CI 0.75–1.57], 1.45 [1.12–1.89], and 1.69 [1.28–2.22] across increasing diet soda consumption categories compared with nonconsumption, respectively). Results were similar when adjusted for change in body weight (data not shown).

With stratification for BMI (<25 vs. ≥25 kg/m^2), HRs were similar in both strata for metabolic syndrome and type 2 diabetes, although there were few incident cases and much larger confidence intervals in the BMI <25 kg/m^2 strata, comparing extreme intake categories for metabolic syndrome (HR 2.2 [95% CI 1.10–4.51] with BMI <25 kg/m^2 and 1.48 [1.07–2.05] with BMI ≥25 kg/m^2) and for type 2 diabetes (1.94 [0.87–4.35] with BMI <25 kg/m^2 and 1.54 [1.15–2.07] with BMI ≥25 kg/m^2).

Sugar-sweetened soda and risk of metabolic syndrome and type 2 diabetes

Although our primary analyses focused on diet soda intake, we also estimated corresponding risks for metabolic syndrome and type 2 diabetes according to consumption of sugar-sweetened soda. Data showed no significant associations between sugar-sweetened soda consumption and risk of either metabolic syndrome 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, although CIs were wide (HR 1.43 [0.79–2.61], 1.76 [1.18–2.63], and 2.23 [1.49–3.34], across increasing diet soda consumption categories compared with nonconsumption, respectively). This result was also true for metabolic syndrome (1.63 [1.13–2.36], 1.36 [1.02–1.81], and 1.81 [1.36- 2.42] across increasing diet soda consumption categories compared with nonconsumption, respectively, n = 1,773).

Metabolic syndrome component

Compared with nonconsumers, individuals consuming ≥1 daily serving of diet soda had a significantly greater risk of developing high waist circumference (≥102 cm if male and ≥88 cm if female) or high fasting glucose (≥100 mg/dl) during follow-up (HR 1.59 [95% CI 1.23–2.07] and 1.28 [1.08–1.52] for high waist circumference and high fasting 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 metabolic syndrome HRs were adjusted for baseline measures of individual metabolic syndrome components. Similarly, the largest amount of attenuation occurred when HRs for incident metabolic syndrome were adjusted for baseline waist circumference or baseline fasting glucose concentration (comparing individuals consuming ≥1 serving of diet soda versus nonconsumers: 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; and 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

Table 3—*Risk of developing metabolic syndrome components according to diet soda intake categories in participants from MESA*

	Rare or never	More often than rare/never but <1 serving/week	≥1 serving/week to <1 serving/day	≥1 serving/day
Blood pressure*				
n	1,990	322	602	449
Cases	512	74	144	113
HR (95% CI)†	1.00 (model 2)	1.07 (0.83–1.37)	1.11 (0.91–1.34)	1.17 (0.95–1.45)
Waist circumference*				
n	1,544	208	399	277
Cases	282	44	93	81
HR (95% CI)†	1.00 (model 2)	1.13 (0.82–1.57)	1.22 (0.95–1.55)	1.59 (1.23–2.07)
HDL cholesterol*				
n	1,881	306	609	434
Cases	604	97	173	127
HR (95% CI)†	1.00 (model 2)	1.12 (0.88–1.44)	0.96 (0.78–1.17)	1.05 (0.84–1.30)
Triglycerides*				
n	2,143	344	666	476
Cases	499	78	156	115
HR (95% CI)†	1.00 (model 2)	1.05 (0.82–1.33)	1.10 (0.91–1.33)	1.04 (0.84–1.28)
Fasting glucose*				
n	2,453	400	793	584
Cases	664	97	215	177
HR (95% CI)†	1.00 (model 2)	0.97 (0.78–1.21)	1.13 (0.96–1.32)	1.28 (1.08–1.52)

*Metabolic syndrome components are defined as follows: high blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking antihypertensive mediation; high waist circumference: ≥102 cm if male or ≥88 cm if female; low HDL cholesterol: <40 mg/dl if male or <50 mg/dl if female; high triglycerides: ≥150 mg/dl; high fasting glucose: ≥100 mg/dl. †Model 2 adjusted for study site, age, sex, race/ethnicity, energy intake education, physical activity, smoking status, pack-years, and weekly supplement use or more.

with respect to risk of metabolic syndrome, metabolic syndrome 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 metabolic syndrome 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).

CONCLUSIONS — In MESA, diet soda consumption was positively associated with both incident metabolic syndrome 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 metabolic syndrome. Consistent with these findings, diet soda was associated with development of high fasting glucose and high waist circumference during follow-up but not with other metabolic syndrome components, suggesting that in this analysis, metabolic syndrome 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 individuals 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. We 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, overconsumption of other foods/beverages may also occur in conjunction with diet beverage consumption owing 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 to maintain weight. Nevertheless, empirical data have not universally supported these hypotheses. Although data from one observational study showed that women who consumed >5.8 g saccharin daily gained slightly more weight than nonconsumers over 2 years (13), experimental data show that participants randomly assigned to dietary regimens that include artificially sweetened foods and beverages do not gain more weight or consume more energy compared with those randomly assigned 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 examinations. Therefore, our data do not indicate that a 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 metabolic syndrome were strongly attenuated when adjusted for these measures of adiposity. Consistent with these data, only the metabolic syndrome 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, several artificial sweeteners for sweetening diet beverages have been used by the soda industry. The sweeteners most commonly used in diet beverages had also changed from the initiation of MESA to the most recent examination. These dynamics make it difficult to attribute our findings to the biological effects of a particular artificial sweetener. Mechanistic studies in randomized, controlled settings addressing how artificial sweeteners consumed from diet beverages affect early markers of metabolic dysfunction are lacking (especially considering true-to-life exposure to multiple sweeteners). Data such as ours and those that preceded ours (1,2), suggest that such research is warranted. Current literature articles provide data on single sweeteners only, mostly aspartame (12,14,16,17,19–24), with a 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 nonconsumers were different in several respects (i.e., regular diet beverage consumers ate more whole grains, fruit, low-fat dairy products, desserts, and coffee but less high-fat dairy products, processed meat, refined grains, and sugar-sweetened soda). These differences are consistent with dietary patterns that have been independently associated with a lower risk of metabolic syndrome or type 2 diabetes (1). Analogously, individuals choosing to consume diet soda probably follow other healthy behaviors that influence metabolic syndrome 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 food frequency questionnaire 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 probably 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.

In summary, daily diet soda consumption was associated with significantly greater risks of two metabolic syndrome components (incident high waist circumference and fasting glucose) and type 2 diabetes in this large, multiethnic cohort. These results corroborate findings from the Atherosclerosis Risk in Communities and Framingham studies and show that 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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