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Original Contribution

Associations of Biomarker-Calibrated Intake of Total Sugars With the Risk of Type 2 Diabetes and Cardiovascular Disease in the Women's Health Initiative Observational Study

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The inconsistent findings from epidemiologic studies relating total sugars (TS) consumption to cardiovascular disease (CVD) or type 2 diabetes (T2D) risk may be partly due to measurement error in self-reported intake. Using regression calibration equations developed based on the predictive biomarker for TS and recovery biomarker for energy, we examined the association of TS with T2D and CVD risk, before and after dietary calibration, in 82,254 postmenopausal women participating in the Women's Health Initiative Observational Study. After up to 16 years of follow-up (1993–2010), 6,621 T2D and 5,802 CVD incident cases were identified. The hazard ratio for T2D per 20% increase in calibrated TS was 0.94 (95% confidence interval (CI): 0.77, 1.15) in multivariable energy substitution, and 1.00 (95% CI: 0.85, 1.18) in energy partition models. Multivariable hazard ratios for total CVD were 0.97 (95% CI: 0.87, 1.09) from energy substitution, and 0.91 (95% CI: 0.80, 1.04) from energy partition models. Uncalibrated TS generated a statistically significant inverse association with T2D and total CVD risk in multivariable energy substitution and energy partition models. The lack of conclusive findings from our calibrated analyses may be due to the low explanatory power of the calibration equations for TS, which could have led to incomplete deattenuation of the risk estimates.

calibration; cardiovascular disease; diabetes; diet; measurement error; total sugars; Women's Health Initiative

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; EP, energy partition; ES, energy substitution; HR, hazard ratio; ME, measurement error; NPAAS, Nutrition and Physical Activity Assessment Study; OS, Observational Study; T2D, type 2 diabetes; TS, total sugars; WHI, Women's Health Initiative.

The development of a predictive biomarker for total sugars (TS) consumption (1) has enabled the study of measurement error (ME) in self-reported TS intake (2) and ME correction in disease association studies (3). Predictive biomarkers are a distinct group of dietary biomarkers that can predict (i.e., estimate) intake after being calibrated for their biases (2). Hence, these biomarkers can be used as reference validation instruments similar to recovery biomarkers, provided their biases have been quantified in an appropriate feeding study.

Type 2 diabetes (T2D) and cardiovascular disease (CVD) are 2 of the most prevalent, largely preventable chronic diseases worldwide (4). Approximately 30.2 million adults in the United States have diabetes; of these cases, 90%–95% are T2D (5), whereas more than 1 in 3 US adults have CVD (including hypertension) (6). Dietary sugars (e.g., TS, sucrose, fructose, glucose) or sources of sugars (e.g., sugar-sweetened beverages) in relation to T2D or CVD risk have long been investigated (7–13). Plausible mechanisms include hyperinsulinemia, insulin resistance, inflammation, and oxidative stress promoted by the glycemic effect of diets high in refined sugars (14). More specifically, de novo lipogenesis in the liver induced by high levels of fructose consumption results in dyslipidemia, insulin resistance, and hyperuricemia (15, 16). In addition, potential excess in energy intake associated with TS consumption elicits indirect

effects of sugars on these 2 outcomes mediated by overweight and obesity (17).

Although establishing the role of TS or individual sugars as nutrients in the etiology of these 2 outcomes poses a challenge (7, 8, 18–20), the adverse evidence for sugar-sweetened beverages, a liquid form of added sugars (21), in relation to CVD (9) and T2D (10) is more consistent. This may result from the fact that sugars in beverages may have more pronounced adverse metabolic effects related to rapid metabolism as compared with sugars in solid foods, which are embedded within the food matrix and thus are slower to enter metabolic pathways (22). Sugars from liquids may also have weaker satiating effect, leading to consumption of larger portion sizes (23). Furthermore, it is plausible that inconsistencies in the evidence arise from differential misreporting of sugars-related intake. Sugar-sweetened beverages come in common, predefined serving sizes; hence, they are generally cognitively easier to report on any self-reporting instrument, whereas estimates of individual sugars are generated through food and nutrient databases from reported intake occasions of multiple food items associated with various levels of ME (24–26).

Using the predictive biomarker of TS, it has been found in several validation studies that self-reports underestimated TS consumption (2, 3, 27) and were associated with attenuation factors that could bias disease relative risks toward the null (i.e., ranging from 1.1 to 1.5 for a true relative risk = 2) (2, 3), even when they are assumed to be free of systematic biases. When dietary validation studies are incorporated within cohorts, adjustment for ME in self-reported intake or observed relative risks can be made (28). When a validation study with objective dietary biomarkers (24) was used in the Women's Health Initiative (WHI) Observational Study (OS) (29), after ME correction, energy intake was associated with increased risk of breast cancer (30), all cancer (31, 32), CVD (33), and T2D (34), and protein intake was associated with increased risk of T2D (34) and decreased risk of frailty (35).

In the current study, we used data from a WHI validation study with the predictive biomarker of TS intake (3) to correct for ME (i.e., to calibrate) self-reported TS in all WHI OS participants and to explore the associations of TS intake with CVD and T2D risk before and after dietary calibration. These associations were explored through 2 energy adjustment methods: energy substitution (ES) and energy partition (EP) models (36, 37).

METHODS

WHI OS Study

The WHI OS is a prospective study involving 93,676 postmenopausal women aged 50–79 years, enrolled during 1993–1998 from 40 clinical centers across the United States. The study design has been described in detail elsewhere (29, 38, 39). Briefly, all participants completed baseline questionnaires inquiring about demographic characteristics, and personal and family medical history. The WHI semiquantitative food frequency questionnaire was used to assess participants' usual diet over the previous 3 months. The food frequency questionnaire included a list of 122 foods or food groups, questions about frequency of intake and portion size, 19 adjustment questions on how foods were prepared, and 4 summary questions on usual intake of fruit, vegetables, and fat added to foods and used in cooking (40). Daily energy and nutrient intake were calculated using the University of Minnesota's Nutrition Data System for Research, version 2005 (Nutrition Coordinating Center, Minneapolis, Minnesota). TS represent the sum of monosaccharides (i.e., glucose, fructose, and galactose) and disaccharides (i.e., sucrose, lactose, and maltose). Participants' smoking and alcohol habits and recreational physical activity were assessed using the WHI Personal Habit Questionnaire (41). To generate activity-related energy expenditure, estimates of recreational physical activity were combined with estimates of housework, yardwork, sitting, and sleeping reported on other WHI questionnaires in metabolic equivalents per week and computed into kilocalories per day, according to the following calculation: total metabolic equivalents per week multiplied by body weight (in kilograms) divided by 7. At baseline, body height and weight, and waist circumference were measured, and body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters) squared.

Nutrition and Physical Activity Assessment Study

The Nutrition and Physical Activity Assessment Study (NPAAS) was an ancillary study nested within the WHI OS in which detailed dietary and physical activity measurements were collected from a representative subsample of the WHI OS participants (24). All participants completed a doubly labeled water protocol, a 24-hour urine collection, and indirect calorimetry, as previously described in detail (24). NPAAS included 450 women participating in WHI OS who were ages 60–91 years at NPAAS baseline (2007–2009) and recruited from 9 WHI clinical centers. Biomarker-based estimates of TS (3), energy, and protein intake (24), ratio of sodium to potassium intake (42), and activity-related energy expenditure (43) were derived as previously reported. Furthermore, for each of these exposures, a calibration equation that regresses log of biomarker-predicted exposure on log of self-reported estimate, along with other personal characteristics, was developed (3, 24, 42, 43).

Ascertainment of outcomes

Follow-up for cases of CVD and T2D was calculated from baseline (1993–1998) until diagnosis and, for noncases, until censoring on September 30, 2010, last follow-up, or death, whichever came first. CVD incident cases were reported annually by a self-administered questionnaire. Reports were then reviewed by local WHI physician adjudicators, who assigned diagnoses on the basis of medical records, death certificates, and autopsy reports, which were then forwarded to central physician adjudicators for independent confirmation (44). CVD outcomes included incident cases from any CVD (total CVD); coronary heart disease (CHD), and stroke. Findings on nonfatal myocardial infarction, coronary death, heart failure, coronary artery bypass graft, percutaneous coronary intervention, ischemic and hemorrhagic stroke are reported in Web Table 1 (available at https://academic.oup.com/aje). T2D included self-reported incident cases identified via annual mailed questionnaires when participants were asked to report if a doctor ever prescribed pills or insulin shots for diabetes after the participant had been enrolled in the study. Substantial agreement between self-report

and medication inventory or medical record-verified T2D was demonstrated in earlier work in this cohort (45, 46).

Analytical data set

From 93,676 participants, we excluded women with implausible self-reported energy intake (<600 or >5,000 kcal/day) on the food frequency questionnaire or missing data on diet (n = 3,662), BMI (n = 1,105), physical activity level (n = 2,861), smoking status (n = 1,351), educational level (n = 767), marital status, postmenopausal hormone therapy use, history of hypertension or hypercholesterolemia (n = 2,111), and those with no follow-up (n = 471). To generate the CVD analytical cohort (n = 64,751), from 82,254 women, we further excluded those with history of CVD at baseline (n = 16,301) and with missing data on CVD-specific model covariates (i.e., history of treated T2D, statin use, aspirin use, family history of CVD) (n = 1,507). For T2D analysis, from 82,254 women, we further excluded prevalent cases of T2D at baseline (n = 3,238) and women with missing data on T2D-specific model covariates (i.e., history of CVD and family history of diabetes) (n = 3,957) for a final T2D analytical cohort of 75,320 women. (Some participants were excluded based on more than one exclusion criterion.)

Statistical analysis

The calibration equations for TS, energy, protein, and ratio of sodium to potassium intake, and activity-related energy expenditure were redeveloped using the NPAAS data by regressing log-transformed biomarker-based values on log-transformed self-reported estimates, along with covariates included in the original respective calibration equations (3, 33, 42, 43) and covariates from the respective disease risk models, in accordance with the standard regression calibration methodology (47, 48). We developed individual calibration equations for age- and energy-adjusted (basic), and multivariable ES and EP models for T2D and CVD (see Web Tables 2–5).

Hazard ratios and 95% confidence intervals for a 20% increase in calibrated or uncalibrated TS intake were estimated by a Cox proportional hazards regression model stratified on age in 5-year categories to allow for different baseline hazards by age category in basic and multivariable models. These hazard ratio estimates were based on linear modeling of the log of hazard ratios on the logarithm of calibrated intake. Based on median intake, a 20% increase corresponds to 18.0 g/1,000 kcal for calibrated and 12.6 g/1,000 kcal for uncalibrated TS.

We report findings from 2 different modeling approaches for energy intake adjustment (36, 37). We used the ES model to investigate the association between TS and outcomes when substituting TS (g/1,000 kcal) for other energy-contributing nutrients not included in the model while keeping total energy intake constant (kcal/day). We used the EP model to investigate the association between TS and outcomes when adding TS along with energy from sugars (g/day) while keeping nonsugars and nonalcohol energy constant (kcal/day), calculated as total energy minus energy from alcohol and energy from TS intake.

Table 1. Baseline Characteristics of Participants in the Women's Health Initiative Observational Study Enrolled During 1993–1998 and Nutrition and Physical Activity Assessment Study Enrolled During 2007–2009

Characteristics	CVD Analytical Cohort				T2D Analytical Cohort			
	WHI OS (n = 64,751)		NPAAS (n = 342)		WHI OS (n = 75,320)		NPAAS (n = 383)	
	No.	%	No.	%	No.	%	No.	%
Age group at screening, years								
≤59	22,300	34.5	239	69.9	24,399	32.4	260	67.9
60–69	28,426	43.9	86	25.1	33,120	44.0	99	25.8
≥70	14,025	21.7	17	5.0	17,801	23.6	24	6.3
White race	55,132	85.1	226	66.1	65,198	86.6	261	68.1
College degree or higher	28,670	44.3	176	51.5	33,314	44.2	205	53.5
Family history of T2D	19,925	30.8	106	31.0	23,632	31.4	123	32.1
Family history of CVD	43,170	66.7	217	63.5	50,803	67.4	237	61.9
Treated hypertension	14,229	22.0	48	14.0	17,829	23.7	57	14.9
Current smokers	3,864	6.0	17	5.0	4,502	6.0	17	4.4
Alcohol intake								
Never or past	17,807	27.5	85	24.9	20,576	27.3	91	23.8
1–6 drinks/week	38,214	59.0	216	63.2	44,530	59.1	244	63.7
≥7 drinks/week	8,730	13.5	41	12.0	10,214	13.6	48	12.5
Use of hormone therapy[a]	30,010	46.3	174	50.9	34,774	46.2	199	51.9
Treated high cholesterol	8,003	12.4	24	7.0	10,549	14.0	27	7.0

Abbreviations: CVD, cardiovascular disease; NPAAS, Nutrition and Physical Activity Assessment Study; OS, Observational Study; T2D, type 2 diabetes; WHI, Women's Health Initiative.

[a] Estrogen alone or estrogen plus progestin user.

Table 2. Geometric Means for Anthropometric and Dietary Characteristics of Participants in the Women's Health Initiative Observational Study Enrolled During 1993–1998 and Nutrition and Physical Activity Assessment Study Enrolled During 2007–2009

Characteristics	CVD Analytical Cohort				T2D Analytical Cohort			
	WHI OS (n = 64,751)		NPAAS (n = 342)		WHI OS (n = 75,320)		NPAAS (n = 383)	
	GM	95% CI[a]	GM	95% CI	GM	95% CI	GM	95% CI
Body mass index[b]	26.50	26.46, 26.54	27.24	26.64, 27.86	26.45	26.41, 26.49	27.00	26.42, 27.59
Waist circumference, cm	83.17	83.07, 83.27	82.97	81.55, 84.41	83.10	83.01, 83.18	82.42	81.08, 83.78
Calibrated total energy, kcal	2,156	2,155, 2,158	2,250	2,223, 2,277	2,173	2,172, 2,175	2,273	2,246, 2,300
Calibrated total sugars density, g/1,000 kcal	95.00	94.60, 95.30	86.40	82.30, 90.70	84.30	84.10, 84.60	78.70	76.20, 81.40
Calibrated protein density, g/1,000 kcal	36.40	36.30, 36.40	35.80	35.30, 36.40	34.70	34.70, 34.70	34.20	33.90, 34.50
Calibrated Na/K	1.33	1.32, 1.33	1.40	1.36, 1.44				
Calibrated AREE, kcal	860	858, 861	978	952, 1,004	854	852, 356	986	962, 1,011

Abbreviations: AREE, activity-related energy expenditure; CI, confidence interval; CVD, cardiovascular disease; GM, geometric mean; Na/K, ratio of sodium to potassium; NPAAS, Nutrition and Physical Activity Assessment Study; T2D, type 2 diabetes; WHI-OS, Women's Health Initiative Observational Study.

[a] Naïve 95% confidence interval for calibrated estimates.

[b] Weight (kg)/height $(m)^2$.

The standard errors for hazard ratios from the models with calibrated estimates were estimated by a bootstrap procedure with 1,000 bootstrap samples, to account for the random variation in calibration equation coefficient estimates. We conducted stratified analyses by BMI (<25.0, 25.0–29.9, or ≥30.0) using multivariable EP models with calibrated TS intake, and we only present findings for the composite CVD outcomes (i.e., total CVD and CHD) because of the limited number of cases from individual outcomes in some strata.

Because participants with hypercholesterolemia, history of hypertension or CVD, or family history of diabetes may have changed their diet because of their increased risk for T2D, the models were repeated after excluding these women (n = 47,109). Furthermore, all CVD models were repeated after excluding cases diagnosed during the first year of follow-up. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina) and R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). The P values for statistical tests were 2 tailed and considered statistically significant at a level of less than 0.05.

RESULTS

Baseline characteristics of the study population in the WHI OS and NPAAS are listed in Tables 1 and 2 (for more detail see Web Table 5). WHI OS participants were older, predominantly white, and had lower BMI compared with participants in NPAAS, which oversampled participants of younger age, race or ethnicities other than non-Hispanic white, and higher BMI (33). The median TS density intake ranged from 60 to 62 g/1,000 kcal before calibration (Web Table 5), and from 79 to 95 g/1,000 kcal after calibration, in WHI OS and NPAAS populations (Table 2).

After up to 16 years of follow-up, a total of 6,621 incident cases of T2D and 5,802 cases of CVD were identified. In calibrated basic and multivariable ES models, TS intake was not associated with T2D risk (Table 3). The hazard ratio estimates for 20% increase in calibrated TS intake remained almost unchanged after adding BMI and waist circumference to the model. In the basic EP model, we detected a statistically significant 22% increase in T2D risk for 20% increase in calibrated TS intake (hazard ratio (HR) = 1.22, 95% confidence interval (CI): 1.09, 1.37). However, the hazard ratio was markedly attenuated toward null in multivariable model (HR = 1.00, 95% CI: 0.83, 1.18) and became lower than 1.0 when BMI and waist circumference were added to the model (Table 3). When using uncalibrated TS intake, we found a statistically significant decrease in T2D risk in multivariable ES (HR = 0.92, 95% CI: 0.90, 0.93) and EP (HR = 0.94, 95% CI: 0.93, 0.95) models. The risk estimates remained statistically significant after the models were adjusted for BMI and waist circumference. In sensitivity analysis, excluding participants with hypercholesterolemia, hypertension, history of CVD, or family history of diabetes did not appreciably change any of the findings (data not shown).

In basic and multivariable ES models, no association between calibrated TS intake and total CVD, CHD, or stroke was detected (Table 4). In multivariable EP models, we found an inverse association between calibrated TS intake and total CVD (per each 20% increase, HR = 0.90, 95% CI: 0.84, 0.97) and CHD risk (HR = 0.89, 95% CI: 0.81, 0.96) only after adjusting for BMI. With regard to other CVD outcomes, we observed inverse

Table 3. Hazard Ratios for Type 2 Diabetes for a 20% Increase in Calibrated and Uncalibrated Intakes of Total Sugars, From Baseline (1993–1998) Through September 30, 2010 (n = 75,320), Women's Health Initiative Observational Study[a,b]

Model	Calibrated Total Sugars[c]				Uncalibrated Total Sugars[c]			
	Energy Substitution		Energy Partition		Energy Substitution		Energy Partition	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age- and energy-adjusted[d]	0.99	0.92, 1.07	1.22	1.09, 1.37	0.93	0.92, 0.95	0.94	0.93, 0.96
Multivariable 1[e]	0.94	0.76, 1.15	1.00	0.85, 1.18	0.92	0.90, 0.93	0.94	0.93, 0.95
Multivariable 2[f]	0.93	0.67, 1.31	0.94	0.87, 1.01	0.95	0.94, 0.97	0.96	0.95, 0.98

Abbreviations: AREE, activity-related energy expenditure; CI, confidence interval; HR, hazard ratio; T2D, type 2 diabetes.

[a] Findings from energy substitution and energy partition models.

[b] n = 6,621 T2D cases.

[c] Models with calibrated total sugars included calibrated estimates of energy intake and AREE, whereas models with uncalibrated total sugars included uncalibrated estimates of those exposures.

[d] Cox models were stratified by 5-year age groups and adjusted for age as a continuous variable and energy intake (total energy intake in energy substitution models; nonsugars and nonalcohol energy in energy partition models).

[e] Additionally adjusted for race and ethnicity (white, black, Hispanic, American Indians, Asian/Pacific Islanders, or other or unknown), marital status (never married, divorced or separated, presently married or living as married, or widowed), educational level (0–8 years, some high school, high school diploma or General Educational Development diploma, school after high school, or college degree or higher), smoking status (never, past smoker, and current smoker), hormone therapy use (never, estrogen alone, and estrogen plus progestin user), history of treated hypertension (yes or no), history of cardiovascular disease (yes or no), family history of T2D (yes or no), history of treated hypercholesterolemia (yes or no), alcohol consumption (never drinker, past drinker, <1 per month, 1–3 per month, 1–6 per week, and ≥7 per week), and AREE.

[f] Multivariable model 1 plus BMI plus waist circumference.

association with coronary death and heart failure in basic ES models, and this association became attenuated toward null in multivariable models (Web Table 1). In basic EP models, a 20% increase in TS intake was associated with a statistically significant increase in risk for coronary artery bypass graft (HR = 1.14, 95% CI: 1.02, 1.27). This association dissipated after adding other covariates (multivariable 1), and become significantly inverse with BMI in the model (multivariable 2). Statistically significant inverse association was also observed for nonfatal myocardial infarction and percutaneous coronary intervention, which remained unchanged after adjusting for BMI. For uncalibrated sugars, we found a weak inverse association for several CVD outcomes in the multivariable ES and EP models (Table 4, Web Table 1). Excluding CVD cases diagnosed within the first year of follow-up did not appreciably change any of the findings (data not shown).

In Table 5, we report hazard ratio estimates for T2D and CVD from EP models with calibrated TS by BMI category. No association was found between calibrated TS intake and T2D risk in any of the BMI strata. There was no association between calibrated TS intake and CVD risk among normal-weight and obese participants; there was some evidence of an inverse association among overweight women only (for total CVD, per each 20% increase, HR = 0.90, 95% CI: 0.81, 1.01; for total CHD, HR = 0.87, 95% CI: 0.76, 0.99).

DISCUSSION

In this analysis in which biomarker-based ME correction was applied to self-reports of TS and energy by WHI OS participants, we found no statistically significant association between TS intake and either T2D or CVD risk. In contrast, analyses with uncalibrated exposures appeared to generate an inverse association with T2D risk and some evidence of inverse association with CVD risk.

In a meta-analysis of 12 prospective cohort studies, no association was found between self-reported TS intake and T2D risk with a pooled relative risk of 0.91 (95% CI: 0.76, 1.09) for participants with highest versus lowest level of intake (11). Only 1 among these cohorts reported an inverse association with T2D risk (49), whereas no association was reported by others (12, 50–53). Similar to our study, Ahmadi-Abhari et al. (50) used ES and EP models, and with neither model did they observe an association between TS consumption and T2D risk. Although we included calibrated protein in our analyses, the lack of biomarkers for fat or complex carbohydrates prevented us from exploring any potential confounding effect from the latter 2 macronutrients, because combining calibrated with uncalibrated energy sources would not have allowed for a meaningful interpretation. In our uncalibrated analyses, TS intake was inversely associated with T2D risk across all the models, whereas this association was no longer evident after calibration. Moreover, there was a statistically significant increase in T2D risk in the model testing the association when adding calibrated TS intake while keeping nonsugars energy constant (EP basic model), though this association was attenuated in multivariable models, and especially when BMI and waist circumference were added to the model. Yet, that, in contrast, we observed no association in the ES models suggests the association observed in the EP model was mediated by energy and, similar to other energy sources, TS intake may be a risk factor for T2D. In our cohort, family history of T2D and personal history of hypercholesterolemia are strong correlates of BMI (a potential mediator in the observed association), which may have led to underestimation of the association between sugars intake and T2D in the multivariable model (without BMI) due to possible overadjustment. An interesting observation was the

Table 4. Hazard Ratios for Cardiovascular Disease for 20% Increase of Calibrated and Uncalibrated Intakes of Total Sugars From Energy Substitution and Energy Partition Models, From Baseline (1993–1998) Through September 30, 2010 (n = 64,751), Women's Health Initiative Observational Study

Model	Calibrated Total Sugars[a]				Uncalibrated Total Sugars[a]			
	Energy Substitution		Energy Partition		Energy Substitution		Energy Partition	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Total CVD[b]								
Age- and energy-adjusted[c]	0.98	0.94, 1.03	1.03	0.95, 1.12	0.96	0.94, 0.97	0.96	0.95, 0.98
Multivariable 1[d]	0.97	0.87, 1.09	0.91	0.80, 1.04	0.97	0.95, 0.99	0.98	0.96, 0.99
Multivariable 2[e]	0.97	0.85, 1.12	0.90	0.84, 0.97	0.98	0.96, 1.00	0.98	0.97, 1.00
Total CHD[f]								
Age- and energy-adjusted	0.99	0.94, 1.04	1.05	0.95, 1.15	0.95	0.93, 0.97	0.96	0.94, 0.97
Multivariable 1	0.96	0.86, 1.07	0.90	0.78, 1.04	0.97	0.95, 0.99	0.98	0.96, 0.99
Multivariable 2	0.96	0.83, 1.11	0.89	0.81, 0.96	0.97	0.95, 1.00	0.98	0.96, 1.00
Total stroke[g]								
Age- and energy-adjusted	0.96	0.92, 1.01	0.98	0.91, 1.05	0.98	0.95, 1.01	0.98	0.96, 1.00
Multivariable 1	1.00	0.85, 1.18	0.97	0.85, 1.10	0.99	0.95, 1.03	0.99	0.96, 1.02
Multivariable 2	1.00	0.84, 1.20	0.95	0.86, 1.06	1.00	0.96, 1.03	0.99	0.96, 1.02

Abbreviations: AREE, activity-related energy expenditure; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] Models with calibrated total sugars included calibrated estimates of energy, protein, and ratio of sodium to potassium intake, and AREE, whereas models with uncalibrated total sugars included uncalibrated estimates of those exposures.

[b] n = 5,802.

[c] Cox models were stratified by 5-year age groups and adjusted for age as a continuous variable and energy intake (total energy intake in energy substitution models; nonsugars and nonalcohol energy in energy partition models).

[d] Additionally adjusted for race and ethnicity (white, black, Hispanic, American Indians, Asian/Pacific Islanders, or other or unknown), educational level (0–8 years, some high school, high school diploma or General Educational Development diploma, school after high school, or college degree or higher), smoking status (never, past smoker, and current smoker), hormone therapy use (never, estrogen alone, and estrogen plus progestin user), history of treated hypertension (yes or no), history of cardiovascular disease (yes or no), family history of T2D (yes or no), history of treated hypercholesterolemia (yes or no), alcohol consumption (never drinker, past drinker, <1 per month, 1–3 per month, 1–6 per week, and ≥7 per week), AREE, and ratio of sodium-to-potassium intake.

[e] Multivariable 1 plus BMI.

[f] n = 4,291.

[g] n = 1,868.

opposite direction in the association of calibrated compared with uncalibrated TS consumption with T2D in the basic EP models, which suggests ME does not always lead to attenuation but can even cause a change of direction in the association.

We observed no association between TS intake and CVD risk in ES models, which suggests other energy sources may be equally important in relation to CVD risk. There was some evidence of a weak inverse association with total CVD and CHD in EP models confined to overweight women only, which may have been due to confounding from other nutrients derived from nutrient-dense foods high in naturally occurring sugars (e.g., fruits, vegetables). The difference in hazard ratio estimates derived from uncalibrated versus calibrated basic EP models implies that increased sugars intake along with increases in energy may increase CVD risk (e.g., coronary artery bypass graft), yet these associations were no longer evident when other confounders were included in the models. In 2 studies, among few prospective studies of European populations, no association was found between sugars intake and total CVD (7) or CHD risk (18), in fully adjusted ES models with BMI. In 1 cohort, borderline increased risk was found for CHD risk (per 29.5 g TS, HR = 1.15, 95% CI: 0.97, 1.36) among men, no association was found in women, and no association with stroke risk was found in either sex (19).

A major strength of our analysis was the use of biomarker-based, ME-corrected estimates of self-reported TS intake and other exposures, which dampens the ME in the main exposure and the effect of residual confounding from important, poorly measured confounders. The prospective design of our analysis prevented recall bias and limited the potential for reverse causality. We explored association using 2 energy adjustment models, which allowed investigation of the association between TS intake and outcomes when substituting TS for isocaloric amount of other macronutrients (ES model), and when increasing TS intake while keeping the amount of other macronutrients fixed (EP model). The hazard ratios were estimated for a 20% increase in TS consumption, which translates into modest changes in diet (i.e., 18 g/1,000 kcal); however, this would mean that even small hazard ratio estimates would still be important at a population level. We report findings from different models on multiple

Table 5. Multivariable Hazard Ratios for Total Cardiovascular Disease, Coronary Heart Disease, and Type 2 Diabetes for a 20% Increase in Calibrated Total Sugars From Energy Partition Models, by Body Mass Index Category, From Baseline (1993–1998) Through September 30, 2010, Women's Health Initiative Observational Study

Disease Outcome	Total No.	BMI[a]								
		<25.0[b]			25.0–29.9[b]			≥30.0[b]		
		No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Total CVD[c]	64,751	1,986	0.95	0.82, 1.11	2,064	0.90	0.81, 1.01	1,752	0.95	0.86, 1.07
CHD[c]	64,751	1,416	0.93	0.77, 1.11	1,511	0.87	0.76, 0.99	1,364	0.95	0.82, 1.10
T2D[d]	75,320	1,318	0.91	0.79, 1.04	2,126	0.90	0.78, 1.04	3,177	0.94	0.86, 1.03

Abbreviations: AREE, activity-related energy expenditure; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; T2D, type 2 diabetes.

[a] Body weight (kg)/height (m)^2.

[b] Total number of participants by BMI category: BMI <25.0: CVD/CHD cohort, n = 27,396, T2D cohort, n = 32,093; BMI = 25.0–29.9: CVD/CHD cohort, n = 21,806, T2D cohort, n = 25,379; BMI ≥30.0: CVD/CHD cohort, n = 15,549, T2D cohort, n = 17,848.

[c] Multivariable models were stratified by 5-year age groups and adjusted for age as a continuous variable, calibrated nonsugars and nonalcohol energy (kcal/day), race and ethnicity (white, black, Hispanic, or other races), educational level (high school or less, more than high school, or college degree or higher), smoking status (never, past smoker, or current smoker), history of treated hypertension (yes or no), treated hypercholesterolemia (yes or no), family history of CVD (yes or no), hormone therapy use (never, estrogen alone, or estrogen plus progestin), alcohol consumption (never drinker, past drinker, <1 per month, 1–3 per month, 1–6 per week, and ≥7 per week), calibrated AREE, and calibrated ratio of sodium to potassium intake.

[d] Multivariable models were stratified by 5-year age groups and adjusted for age as continuous variable, calibrated nonsugars and nonalcohol energy (kcal/day), ace and ethnicity (white, black, Hispanic, American Indians, Asian/Pacific Islanders, or other or unknown), marital status (never married, divorced or separated, presently married or living as married, and widowed), educational level (0–8 years, some high school, high school diploma or General Educational Development diploma, school after high school, or college degree or higher), smoking status (never, past smoker, and current smoker), hormone therapy use (never, estrogen alone, and estrogen plus progestin user), history of treated hypertension (yes or no), history of cardiovascular disease (yes or no), family history of T2D (yes or no), history of treated hypercholesterolemia (yes or no), alcohol consumption never drinker, past drinker, <1 per month, 1–3 per month, 1–6 per week, and ≥7 per week), calibrated AREE, and calibrated protein intake (g/day).

outcomes, thus some of the findings may have occurred due to a chance. Yet, this is an exploratory, rather than confirmatory, analysis of the effect of ME on the investigated associations. We acknowledge that some selection bias may have occurred, if data were not missing completely at random, which is unlikely, however, given the prospective nature of the analysis.

Although we used ME-corrected estimates for some important confounders, we still lacked calibrated intake for other nutrients for which no biomarkers were available (e.g., fat, dietary fiber), hence we could not control for those. The original calibration equation for TS developed in NPAAS explained only small proportion of variation in "true" sugars intake (6%–18% for absolute TS and 29%–40% for TS density) (3), possibly resulting in incomplete ME correction. In addition, the relatively small size of NPAAS decreased the precision of the risk estimates. The TS biomarker was developed in 2 highly controlled feeding studies conducted in the United Kingdom (1, 54). Although the biomarker was sensitive to intake, and had good reproducibility and high predictive potential, its biases were estimated on the basis of 13 participants consuming their usual diet under controlled conditions in a UK-based study (2). In this application, therefore, we assumed that the biomarker's biases do not substantially change from 1 population to another, thus the equation for biomarker correction or calibration is transferrable and can be applied to a US population (2, 3). This assumption has yet to be investigated under controlled conditions (55). Energy intake was a strong risk factor for T2D and CVD in this cohort when using calibrated energy (per 20% increase, for T2D, multivariate HR = 4.17, 95% CI: 2.68, 6.49; for total CVD, HR = 1.49, 95% CI: 1.23, 1.81) but not when using uncalibrated intake (for T2D, HR = 1.06, 95% CI: 1.04, 1.07; for total CVD, HR = 1.00, 95% CI: 0.99, 1.01) (32). Hence, sugars could be contributing to disease risk through provision of unnecessary energy, as suggested from our basic EP models. The lack of associations in multivariable models may be due to incomplete ME correction, and population-specific biomarker calibration equations may be needed to correct for biomarker's biases. Finally, the biomarker measures total, rather than added sugars; hence, the negative confounding from beneficial micronutrients and bioactive compounds derived from fruit and vegetables, sources of naturally occurring sugars is very likely, and may have counterbalanced the influence of TS intake per se. Furthermore, sugars encapsulated within the food cellular structure may have different metabolic effects than sugars in processed foods high in energy density and depleted of micronutrients (22, 56).

In conclusion, using biomarker-based calibrated intake estimates, no association was observed between TS intake and either T2D or CVD risk in the postmenopausal women in this study, though we cannot rule out that sugars could be contributing to T2D and CVD risk through provision of excess energy. Low explanatory power of the calibration equations for TS intake may have led to incomplete ME correction and incomplete deattenuation of the risk estimates. Additional research on the performance of the sugars biomarker in the US population is needed to better characterize its use and to verify the calibration equations applied here.

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