

## Original Investigation

# Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults

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**IMPORTANCE** Epidemiologic studies have suggested that higher intake of added sugar is associated with cardiovascular disease (CVD) risk factors. Few prospective studies have examined the association of added sugar intake with CVD mortality.

**OBJECTIVE** To examine time trends of added sugar consumption as percentage of daily calories in the United States and investigate the association of this consumption with CVD mortality.

**DESIGN, SETTING, AND PARTICIPANTS** National Health and Nutrition Examination Survey (NHANES, 1988-1994 [III], 1999-2004, and 2005-2010 [n = 31 147]) for the time trend analysis and NHANES III Linked Mortality cohort (1988-2006 [n = 11 733]), a prospective cohort of a nationally representative sample of US adults for the association study.

**MAIN OUTCOMES AND MEASURES** Cardiovascular disease mortality.

**RESULTS** Among US adults, the adjusted mean percentage of daily calories from added sugar increased from 15.7% (95% CI, 15.0%-16.4%) in 1988-1994 to 16.8% (16.0%-17.7%;  $P = .02$ ) in 1999-2004 and decreased to 14.9% (14.2%-15.5%;  $P < .001$ ) in 2005-2010. Most adults consumed 10% or more of calories from added sugar (71.4%) and approximately 10% consumed 25% or more in 2005-2010. During a median follow-up period of 14.6 years, we documented 831 CVD deaths during 163 039 person-years. Age-, sex-, and race/ethnicity-adjusted hazard ratios (HRs) of CVD mortality across quintiles of the percentage of daily calories consumed from added sugar were 1.00 (reference), 1.09 (95% CI, 1.05-1.13), 1.23 (1.12-1.34), 1.49 (1.24-1.78), and 2.43 (1.63-3.62;  $P < .001$ ), respectively. After additional adjustment for sociodemographic, behavioral, and clinical characteristics, HRs were 1.00 (reference), 1.07 (1.02-1.12), 1.18 (1.06-1.31), 1.38 (1.11-1.70), and 2.03 (1.26-3.27;  $P = .004$ ), respectively. Adjusted HRs were 1.30 (95% CI, 1.09-1.55) and 2.75 (1.40-5.42;  $P = .004$ ), respectively, comparing participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugar with those who consumed less than 10.0% of calories from added sugar. These findings were largely consistent across age group, sex, race/ethnicity (except among non-Hispanic blacks), educational attainment, physical activity, health eating index, and body mass index.

**CONCLUSIONS AND RELEVANCE** Most US adults consume more added sugar than is recommended for a healthy diet. We observed a significant relationship between added sugar consumption and increased risk for CVD mortality.

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Consumption of added sugar, including all sugars added in processing or preparing foods, among Americans aged 2 years or older increased from an average of 235 calories per day in 1977-1978 to 318 calories per day in 1994-1996. This change was mainly attributed to the increased consumption of sugar-sweetened beverages.<sup>1</sup> Although the absolute and percentage of daily calories derived from added sugars declined between 1999-2000 and 2007-2008, consumption of added sugars remained high in US diets, especially among children.<sup>2</sup> Recommendations for added sugar consumption vary substantially. The Institute of Medicine recommends that added sugar make up less than 25% of total calories,<sup>3</sup> whereas the World Health Organization recommends less than 10%.<sup>4</sup> The American Heart Association recommends limiting added sugars to less than 100 calories daily for women and 150 calories daily for men.<sup>5</sup> The 2010 *Dietary Guidelines for Americans*<sup>6</sup> recommend limiting total intake of discretionary calories, which include added sugars and solid fats, to 5% to 15% of daily caloric intake. Randomized clinical trials and epidemiologic studies have shown that individuals who consume higher amounts of added sugar, especially sugar-sweetened beverages, tend to gain more weight<sup>7</sup> and have a higher risk of obesity,<sup>2,8-13</sup> type 2 diabetes mellitus,<sup>8,14-17</sup> dyslipidemias,<sup>18,19</sup> hypertension,<sup>20,21</sup> and cardiovascular disease (CVD).<sup>14,22</sup> Most previous studies have focused on sugar-sweetened beverages but not total added sugar, and none of these studies has used nationally representative samples to examine the relationship between added sugar intake and CVD mortality.

In the present study, we examined time trends of consumption of added sugar as percentage of total daily calories using a series of national representative samples. In addition, we investigated the association of this consumption with CVD mortality using a prospective cohort of a nationally representative sample of US adults.

## Methods

### National Health and Nutrition Examination Survey

The National Health and Nutrition Examination Survey (NHANES) comprises a series of cross-sectional, stratified, multistage probability surveys of the civilian, noninstitutionalized US population. The NHANES was conducted periodically before 1994; beginning in 1999, it became a continuous program, with every 2 years representing 1 cycle. Each survey participant completed a household interview and underwent a physical examination at a mobile examination center. Detailed descriptions of NHANES methods are published elsewhere.<sup>23,24</sup> NHANES III and NHANES 1999-2010 underwent institutional review board approval and included written informed consent.

The present study comprised 2 components: a trends analysis of added sugar consumption and an association study of this consumption with CVD mortality. For the trend analysis, we used data from NHANES III (1988-1994) and from the continuous NHANES surveys (1999-2004 and 2005-2010). For NHANES III, of 16 274 nonpregnant adults aged 20 years or older, we excluded 588 participants with incomplete data on

first-day 24-hour dietary recall; 1321 who reported a history of myocardial infarction, stroke, or congestive heart failure; 996 who had diagnosed diabetes mellitus or were taking diabetes medications; and 452 who had cancer at baseline. We also excluded 279 participants with a body mass index (BMI) less than 18.5 (calculated as weight in kilograms divided by height in meters squared) and 905 with missing values on covariates, leaving 11 733 adults for analysis. For NHANES 1999-2004, we started with 13 422 nonpregnant adults and excluded the following numbers of participants for the same reasons described for the 1988-1994 data: 740, 1560, 931, 757, 352, and 296, respectively, leaving 8786 participants for study. For NHANES 2005-2010, we started with 16 089 nonpregnant adults and excluded 826, 1733, 1358, 952, 265, and 327 individuals, respectively, leaving a study population of 10 628.

### NHANES III Linked Mortality Files (1988-2006)

For the association analysis between the added sugar and the risk of CVD mortality, we used NHANES III (1988-1994) Linked Mortality Files (n = 11 733) that were linked through 2006 with a probabilistic matching algorithm to the National Death Index to determine the mortality status. Follow-up of participants continued until death attributable to CVD, with censoring at the time of death for those who died from causes other than CVD. Participants not matched with a death record were considered to be alive through the entire follow-up period. A detailed description of this methodology has been published elsewhere.<sup>25,26</sup> The *International Statistical Classification of Diseases, 10th Revision* was used to identify participants for whom CVD (codes I00-I78) was listed as the underlying cause of death.

### Estimating Usual Percentage of Calories From Added Sugar

Added sugars include all sugars used in processed or prepared foods, such as sugar-sweetened beverages, grain-based desserts, fruit drinks, dairy desserts, candy, ready-to-eat cereals, and yeast breads, but not naturally occurring sugar, such as in fruits and fruit juices. We used 24-hour dietary recall to estimate intake of added sugar. All NHANES participants who received physical examinations provided a single 24-hour dietary recall through in-person interviews.<sup>27</sup> Availability of second dietary recall varied by time period. In NHANES III, approximately 8% of the adult participants provided a second dietary recall; from 1999 to 2002, second recalls were not available. In 2003-2004 and 2005-2010, 93% and 88% of participants participated in second dietary surveys through the telephone interviews 3 to 10 days after mobile examination center interviews.

Nutrient intake from foods was estimated with the corresponding US Department of Agriculture Food and Nutrient Databases for Dietary Studies (FNDDSs).<sup>28</sup> However, FNDDSs do not include information on added sugar for many foods. To estimate the intake of added sugar, we merged individual food files from NHANES with the MyPyramid Equivalent Database (MPED).<sup>29</sup> The MPED has 2 versions; we merged the NHANES III and NHANES 1999-2002 individual foods files with MPED 1.0 and NHANES 2003-2004 and 2005-2010 food files with MPED 2.0 to calculate intake of added sugars.<sup>29,30</sup> Of 5440 unique US Department of Agriculture food codes (8-digit codes)

in NHANES 2005-2010, 5030 of these foods were available from MPED 2.0. We matched the remaining 410 foods to the nearest food codes (most of the matched food codes differed by the last 2 digits) to estimate added sugar content. For example, the food code 52302020 (muffin, fruit and/or nut, low fat) was matched to 52302010 (muffin, fruit and/or nut). A detailed description of the MPED and estimates of added sugar from foods are published elsewhere.<sup>29</sup>

Data from single 24-hour dietary recalls are subject to measurement errors caused by day-to-day variation in intakes,<sup>31,32</sup> which tends to attenuate the association.<sup>33</sup> To correct for measurement errors, we used a method developed by the National Cancer Institute (NCI) that can be used to estimate the distribution of the usual percentage of calories from added sugar in the population.<sup>34</sup> This method also can be used to examine the nutrient-disease association corrected for measurement error, also known as the *regression calibration*.<sup>35</sup> The NCI method requires that at least some respondents have multiple days of nutrient values to estimate the within- and between-individual variations.<sup>34,36</sup> For the trend analysis, the models included the following covariates: day of the week when 24-hour recall was collected (weekday vs weekends), age, sex, and race/ethnicity.<sup>36</sup> For the association analysis, we also included educational attainment, smoking status, alcohol consumption, antihypertensive medication use, physical activity, family history of CVD, and 1995 Healthy Eating Index (HEI) scores.<sup>36,37</sup>

The covariates included race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational attainment (<12, 12, or >12 years of education), smoking status (never, former, or current), alcohol consumption (0, <3, or ≥3 drinks/wk), physical activity (0, <5, or ≥5 times/wk of moderate-intensity to vigorous activities), BMI (<25, 25 to <30, or ≥30), family history of CVD (yes/no), and antihypertensive medication use (yes/no). Systolic blood pressure and total serum cholesterol (milligrams per deciliter) were included as continuous variables. The HEI includes 10 components: fruits, vegetables, grains, dairy, meats, fats, saturated fat, cholesterol, sodium, and dietary variety. The total score ranges from 0 to 100, with a higher score indicating a healthier diet.<sup>37</sup>

### Statistical Analysis

We calculated the weighted mean and 95% CI of the usual percentage of calories from added sugar across categories of selected covariates for NHANES III (1988-1994), 1999-2004, and 2005-2010. We also estimated the percentage of the population who consumed 10% or more<sup>4</sup> or 25% or more<sup>3</sup> of calories from added sugar. We conducted the pairwise 2-tailed *t* tests to identify the difference in means and prevalence across surveys.

We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% CIs for CVD mortality. Because the observed association between percentage of calories from added sugar and CVD mortality appeared to be nonlinear ( $P < .05$  for linearity), we used the Box-Cox transformation, with  $\lambda = 2.5$  when estimating the usual percentage of calories from added sugar using the NCI method.<sup>35</sup> To

present the results, we calculated the 10th, 30th, 50th, 70th, and 90th percentiles' distribution of the estimated added sugar intake as the middle value of each quintile. We estimated the adjusted HRs by comparing the middle values of each quintile (Q) with the lowest quintile as reference (Q5, Q4, Q3, and Q2 vs Q1).<sup>35,38</sup> To examine the association between added sugar intake and CVD mortality by different cut points, ie, less than 10% by the World Health Organization (in line with the American Heart Association's recommendation)<sup>4,5</sup> and less than 25% by the Institute of Medicine,<sup>3</sup> we estimated the adjusted HRs by comparing participants who consumed 25% or more, more than 10%, and less than 25% of their calories from added sugar with those who consumed less than 10% of their calories from added sugar. We estimated age-, sex-, and race/ethnicity-adjusted HRs as well as the multivariable-adjusted HRs including age, sex, race/ethnicity, educational attainment, smoking status, alcohol consumption, antihypertensive medication use, physical activity level, family history of CVD, HEI score, BMI, systolic blood pressure, total serum cholesterol, and total calories. We also determined the results of stratified analysis by age group (<60 years vs ≥60 years), sex, race/ethnicity, educational attainment (<12 vs ≥12 years), physical activity (≥5 times/wk of moderate-intensity vs vigorous activities vs others), HEI score (top 50% [score ≥63.5] vs other), and BMI (normal vs overweight/obese). We calculated the covariates-adjusted number needed to harm associated with each quintile of added sugar intake at 15-years of follow-up (15 years represents the median follow-up),<sup>39</sup> and the 95% CI of the number needed to harm was based on 2.5th and 97.5th percentile values of 500 rescaled bootstrap weights.<sup>40,41</sup>

The proportional hazards assumption of the Cox models was evaluated with Schoenfeld residuals, which revealed no significant departures from proportionality in hazards over time. We tested for interactions of the usual percentage of calories from added sugar with covariates by including the interaction terms in the Cox models based on Satterthwaite-adjusted *F* tests.<sup>42,43</sup>

We conducted several sensitivity analyses (Supplement [eAppendix and eTables 1-7]). All analyses were conducted with SAS, version 9.3 (SAS Institute, Inc) or SUDAAN, version 11, to take into account the complex sampling design.<sup>43</sup> All tests were 2-sided, and  $P < .05$  was considered statistically significant.

## Results

Of participants included in the study from the NHANES III (1988-1994) ( $n = 11\,733$ ), NHANES 1999-2004 ( $n = 8786$ ), and NHANES 2005-2010 ( $n = 10\,628$ ), the proportion of non-Hispanic whites decreased from 76.3% in 1988-1994 to 69.6% in 2005-2010 ( $P = .004$ ) and the Mexican American proportion increased from 5.1% to 9.0% in 2005-2010 ( $P < .001$ ). The mean percentage of calories from added sugar increased from 15.7% (95% CI, 15.0%-16.4%) in 1988-1994 to 16.8% (16.0%-17.7%;  $P < .02$ ) in 1999-2004 and decreased to 14.9% (14.2%-15.5%;  $P < .001$ ) in 2005-2010 (Table 1). Most adults consumed 10% or more of calories from added sugar (71.4%), and

Table 1. Estimated Mean, 10% or More, and 25% or More of Calories Participants Consumed From Added Sugar<sup>a</sup>

Characteristic	NHANES 1988-1994 <sup>b</sup>				NHANES 1999-2004 <sup>b</sup>				NHANES 2005-2010 <sup>b</sup>			
	No. of Participants	Mean (95% CI)			No. of Participants	Mean (95% CI)			No. of Participants	Mean (95% CI)		
		% of Calories	% Who Consumed ≥10% Calories	% Who Consumed ≥25% Calories		% of Calories	% Who Consumed ≥10% Calories	% Who Consumed ≥25% Calories		% of Calories	% Who Consumed ≥10% Calories	% Who Consumed ≥25% Calories
All participants	11 733	15.7 (15.0-16.4)*	78.1 (73.8-82.4)*	10.3 (6.9-13.8)*	8786	16.8 (16.0-17.7)†	77.0 (74.1-79.9)*	16.6 (13.6-19.6)†	10 628	14.9 (14.2-15.5)‡	71.4 (68.6-74.1)†	9.9 (7.6-12.3)*
Age, y												
<60	8835	16.3 (15.5-17.0)*	80.5 (76.1-84.9)*	11.6 (8.0-15.3)*	6651	17.4 (16.5-18.2)†	79.1 (76.1-82.2)*	18.1 (14.9-21.3)†	8264	15.1 (14.4-15.8)‡	72.4 (69.5-75.3)†	10.4 (7.9-12.8)*
≥60	2898	13.3 (12.5-14.0)*	66.7 (61.4-72.0)*	4.6 (2.1-7.0)*	2135	13.7 (13.0-14.5)*	65.0 (61.0-68.9)*	8.0 (5.8-10.3)†	2364	13.6 (13.0-14.2)*	65.4 (62.4-68.4)*	7.0 (5.2-8.8)*
Sex												
Men	5639	15.7 (14.9-16.6)*	78.1 (73.3-83.0)*	10.4 (6.9-13.9)*	4426	17.0 (16.2-17.9)†	77.7 (74.6-80.8)*	17.2 (14.1-20.2)†	5283	15.0 (14.3-15.7)‡	72.1 (68.8-75.4)†	10.3 (8.1-12.5)*
Women	6094	15.7 (14.9-16.5)*	78.0 (73.7-82.4)*	10.4 (6.7-14.1)*	4360	16.7 (15.7-17.7)*	76.1 (72.5-79.8)*	16.2 (12.7-19.7)†	5345	14.7 (13.9-15.5)†	70.6 (67.5-73.7)†	9.5 (6.9-12.2)*
Race/ethnicity												
Non-Hispanic white	4802	15.7 (14.9-16.5)*	78.3 (74.0-82.7)*	10.1 (6.3-13.9)*	4220	16.6 (15.6-17.5)*	76.2 (72.9-79.5)*	15.6 (12.1-19.1)†	4891	14.6 (13.8-15.5)†	70.8 (67.3-74.2)†	9.1 (6.4-11.9)*
Non-Hispanic black	3233	17.9 (17.3-18.6)*	86.4 (82.1-90.6)*	16.9 (13.3-20.0)*	1719	19.8 (18.6-21.0)†	85.9 (82.2-89.7)*	25.9 (21.5-30.3)†	2123	17.5 (16.4-18.5)*	81.9 (78.0-85.9)†	16.9 (13.4-20.4)*
Mexican American	3217	15.6 (14.9-16.3)*	78.0 (72.6-83.4)*	9.7 (6.7-12.7)*	2123	17.2 (15.8-18.7)†	78.7 (74.8-83.7)*	17.6 (12.7-22.5)†	2139	15.8 (15.0-16.6)*	75.8 (71.9-79.7)*	11.9 (9.5-14.4)*
Other	481	12.9 (11.1-14.7)*	63.9 (52.0-75.8)*†	4.3 (1.3-7.3)*	724	15.4 (13.8-17.1)†	71.9 (65.1-78.6)*	12.5 (7.8-17.1)†	1475	12.6 (11.7-13.6)*	60.0 (54.1-66.0)†	5.3 (3.5-7.0)*
Educational attainment, y												
0-11	4318	15.1 (14.5-15.8)*	75.1 (70.4-79.9)*	9.0 (5.9-12.1)*	2617	16.8 (16.0-17.6)†	76.6 (73.5-79.6)*	16.6 (13.9-19.3)†	2822	15.0 (14.5-15.5)*	72.1 (69.8-74.4)†	10.4 (8.5-12.3)*
12	3777	15.9 (15.1-16.6)*	78.8 (74.6-83.0)*	10.7 (7.1-14.2)*	2109	16.9 (16.1-17.8)†	77.2 (74.1-80.3)*	16.9 (13.6-20.2)†	2549	14.9 (14.2-15.6)‡	71.7 (68.7-74.6)†	10.1 (7.8-12.4)*
≥12	3638	15.9 (15.1-16.7)*	79.0 (74.5-83.5)*	10.7 (7.0-14.3)*	4060	16.8 (16.0-17.7)*	77.1 (74.1-80.1)*	16.5 (13.3-19.7)†	5257	14.8 (14.1-15.5)†	71.1 (68.1-74.1)†	9.8 (7.4-12.2)*
Smoking status												
Current	3145	16.3 (15.5-17.0)*	80.5 (76.1-84.8)*	11.7 (8.0-15.5)*	2117	17.4 (16.5-18.3)†	79.1 (76.2-82.0)*	18.2 (14.7-21.6)†	2472	15.2 (14.5-16.0)‡	73.0 (70.0-76.0)†	10.7 (8.2-13.3)*
Former	2670	15.0 (14.3-15.7)*	75.0 (70.4-79.6)*	8.6 (5.4-11.9)*	1985	15.8 (15.0-16.6)*	73.1 (69.9-76.4)*	13.7 (10.7-16.6)†	2239	14.4 (13.8-15.1)†	69.4 (66.7-72.2)†	8.8 (6.6-11.1)*
Never	5918	15.8 (15.1-16.5)*	78.1 (73.8-82.4)*	10.6 (7.1-14.1)*	4684	17.1 (16.3-17.9)†	77.6 (74.7-80.4)*	17.3 (14.3-20.3)†	5917	14.9 (14.3-15.5)‡	71.6 (68.9-74.3)†	10.0 (7.8-12.2)*

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NHANES, National Health and Nutrition Examination Survey.

<sup>a</sup> Among US adults 20 years or older: NHANES, 1988-1994, 1999-2004, and 2005-2010. *P* values are presented for difference across the categories of

selected covariates within each NHANES. Pairwise *P* values are presented. All tests were 2-tailed and based on *t* tests.

<sup>b</sup> The mean usual percentage or prevalence of 10% or more or 25% or more of calories from added sugar across the NHANES surveys that were not sharing a common symbol (\*, †, or ‡) were significantly different at *P* < .05 based on *t* test.

approximately 10% consumed 25% or more of calories from added sugar in 2005-2010. Intake was higher among individuals younger than 60 years, non-Hispanic blacks, and never smokers (Table 1).

Among the 11 733 participants who met the eligibility criteria for mortality analysis in NHANES III (1988-2006), 831 CVD

deaths during 163 039 person-years of follow-up (median follow-up, 14.6 years) were documented. After multivariable adjustment, compared with the lowest quintile, HRs were 1.07 (95% CI, 1.02-1.12), 1.18 (1.06-1.31), 1.38 (1.11-1.70), and 2.03 (1.26-3.27) (*P* = .004) (Table 2). The adjusted HRs were 1.30 (1.09-1.55) and 2.75 (1.40-5.42) comparing participants who con-

**Table 2. Adjusted HR of CVD Mortality According to Usual Percentage of Calories From Added Sugar<sup>a</sup>**

Characteristic	Midvalue of Quintiles of Usual Percentage of Calories From Added Sugar					P Value <sup>b</sup>
	Q1 (7.4%)	Q2 (11.4%)	Q3 (14.8%)	Q4 (18.7%)	Q5 (25.2%)	
Range (0-100)/usual percentage, %	0 to <9.6	9.6 to <13.1	13.1 to <16.7	16.7 to <21.3	≥21.3	
HR (95% CI)						
Adjusted only for age, sex, race/ethnicity	1 [Ref]	1.09 (1.05 to 1.13)	1.23 (1.12 to 1.34)	1.49 (1.24 to 1.78)	2.43 (1.63 to 3.62)	<.001
Fully adjusted <sup>c</sup>	1 [Ref]	1.07 (1.02 to 1.12)	1.18 (1.06 to 1.31)	1.38 (1.11 to 1.70)	2.03 (1.26 to 3.27)	.004
Adjusted NNH at 15-y follow-up <sup>d</sup>		265 (166 to 715)	109 (67 to 297)	53 (33 to 152)	22 (13 to 66)	

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; NNH, number needed to harm; Q, quintile; Ref, reference.

<sup>a</sup> Data on US adults 20 years or older from the National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006. There were 831 deaths due to CVD in 11 733 participants (163 039 total person-years).

<sup>b</sup> P value for testing significant association between the usual percentage of calories from added sugar and CVD mortality based on Satterthwaite F test; all tests are 2-tailed.

<sup>c</sup> Adjusted for age, sex, race/ethnicity, educational attainment, smoking status,

alcohol consumption, physical activity level, antihypertensive medication use, family history of CVD, Healthy Eating Index score, body mass, systolic blood pressure, total serum cholesterol, and total calories intake.

<sup>d</sup> The NNH was estimated at 15 years of follow-up (15 years was approximately the median follow-up) adjusted for age, sex, race/ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, antihypertensive medication use, family history of CVD, healthy eating index score, body mass index, systolic blood pressure, total serum cholesterol, and total calories intake.

**Table 3. Adjusted HR of CVD Mortality Comparing Percentage of Calories From Added Sugar Greater Than or Equal to 10% or 25% With Less Than 10%<sup>a</sup>**

Characteristic	Midvalue of Usual Percentage of Calories From Added Sugar <sup>b</sup>			P Value <sup>c</sup>
	5.0%	17.5%	28.7%	
Range (0-100)/usual percentage, %	0 to <10.0	10.0 to <25.0	≥25.0	
HR (95% CI)				
Adjusted only for age, sex, race/ethnicity	1 [Ref]	1.39 (1.20 to 1.62)	3.55 (2.00 to 6.29)	<.001
Fully adjusted <sup>d</sup>	1 [Ref]	1.30 (1.09 to 1.55)	2.75 (1.40 to 5.42)	.004

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; Ref, reference.

<sup>a</sup> Data on US adults 20 years or older from the National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006. There were 831 deaths due to CVD in 11 733 participants (163 039 total person-years).

<sup>b</sup> Among the participants who consumed 25.0% or more of calories from added sugar, we used the 95th percentile value (28.7%) as a proxy of the midvalue.

<sup>c</sup> P value for testing significant association between the usual percentage of

calories from added sugar and CVD mortality based on the Satterthwaite F test; all tests are 2-tailed.

<sup>d</sup> Adjusted for age, sex, race/ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, antihypertensive medication use, family history of CVD, Healthy Eating Index score, body mass index, systolic blood pressure, total serum cholesterol, and total calories intake.

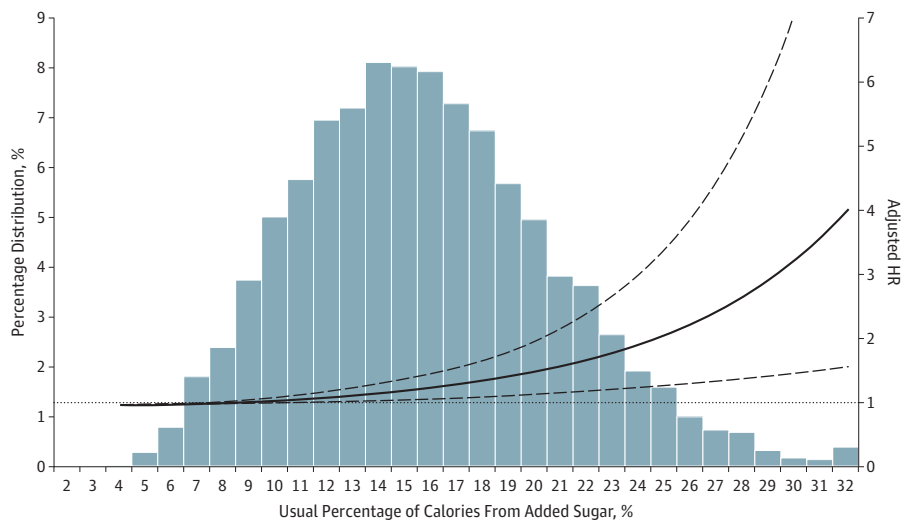
sumed 10% to 24.9% or 25% or more of calories from added sugar with those who consumed less than of 10% of calories from added sugar (Table 3). The risk of CVD mortality increased exponentially with increasing usual percentage of calories from added sugar (Figure 1) (P = .004). The number needed to harm at 15 years of follow-up (median follow-up) reduced from 265 (95% CI, 166-715) to 22 (13-66) (Table 2).

The observed association between usual percentage of calories from added sugar and increased risk of CVD mortality was largely consistent across age group, sex, race/ethnicity (except among non-Hispanic blacks), educational attainment, physical activity level, HEI score, and BMI (Figure 2 and Supplement [eTable 1 and eFigure]). However, we observed a marginally significant interaction between percentage of calories from added sugar and race/ethnicity (P = .09), and the pattern of this association was observed in other groups but not among non-Hispanic blacks (Supplement [eTable 1]). Compared with the participants who consumed less than 10% of calories from added sugar (same as in Q1), those who consumed above the thresholds of 10% or 25% of calories from added sugar were younger; more likely

to be non-Hispanic black; less likely to be currently smoking; had lower levels of physical activity, total serum cholesterol, systolic blood pressure, HEI, American Heart Association healthy diet score,<sup>44</sup> and antihypertensive medication use; and had higher intake of sugar-sweetened beverages and prevalence of family history of CVD (Supplement [eTable 2]). Participants who consumed added sugar exceeding the recommendations, especially 25% or more of calories from added sugar, had a higher percentage of calories from the sugar/sweets/beverage group and a lower percentage of calories from all other food groups except milk products (Supplement [eTable 2]).

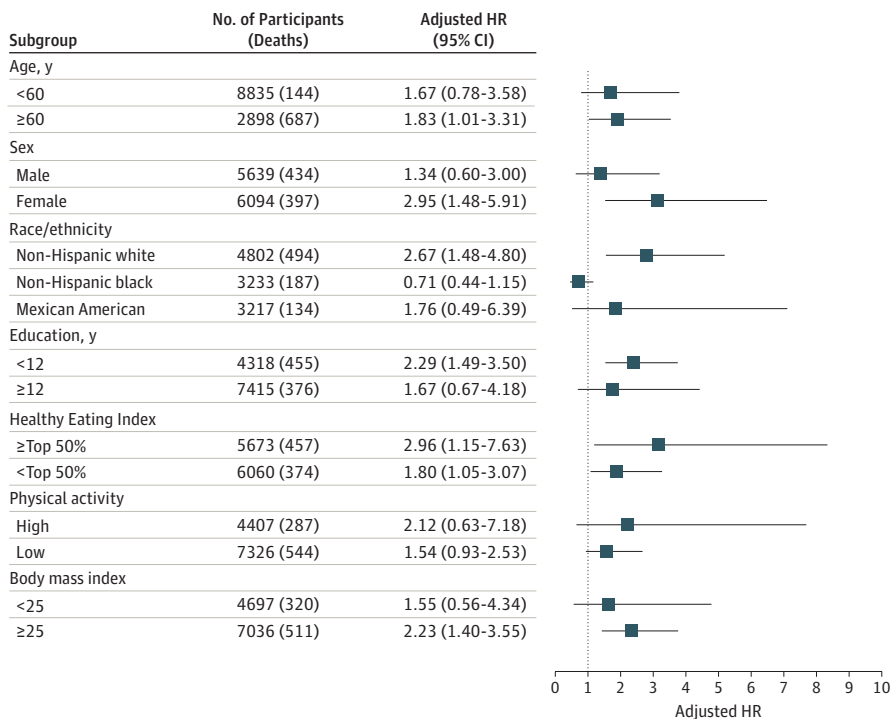
As expected, the association using only a single-day 24-hour recall was attenuated but remained significant (Supplement [eTable 3]). In the analysis including all NHANES III participants with nonmissing covariates (n = 14 338), the association was moderately attenuated (Supplement [eTable 4]). In the fully adjusted model, the HR for total mortality was 1.28 (95% CI, 0.94-1.75) in the highest quintile (Supplement [eTable 5]). Detailed analysis between added sugar intake and each component of the HEI suggested that added sugar in-

**Figure 1. Adjusted Hazard Ratio (HR) of the Usual Percentage of Calories From Added Sugar for Cardiovascular Disease Mortality Among US Adults 20 Years or Older: National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006**



Histogram of the distribution of usual percentage of calories from added sugar in the population. Lines show the adjusted HRs from Cox models. Midvalue of quintile 1 (7.4%) was the reference standard. The model was adjusted for age, sex, race/ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, family history of cardiovascular disease, antihypertensive medication use, Healthy Eating Index score, body mass index, systolic blood pressure, total serum cholesterol, and total calories. Solid line indicates point estimates; dashed lines indicate 95% CIs.

**Figure 2. Adjusted Hazard Ratio (HR) of Cardiovascular Disease Mortality Comparing Quintile 5 With Quintile 1 of Usual Percentage of Calories From Added Sugar by Selected Characteristics Among US Adults 20 Years or Older: National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006**



For the Healthy Eating Index score, the top 50% or higher included the participants with a score of 63.5 or more; high physical activity included the participants who had moderate intensity to vigorous activities 5 or more times per week. Limit lines indicate 95% CI. Body mass index is calculated as weight in kilograms divided by height in meters squared.

take was moderately and negatively correlated with total grain, vegetable, meat, and variety components ( $r = -0.06, -0.20, -0.12,$  and  $-0.19,$  respectively;  $P < .05$ ) and moderately and positively correlated with total fat and cholesterol intake ( $r = 0.17$  and  $0.08;$   $P < .05$ ). However, HRs remained largely unchanged after adjusting each component of the HEI (Supple-

ment [eTable 6]). We observed a significant association between sugar-sweetened beverage consumption and risk of CVD mortality, with an adjusted HR of 1.29 (95% CI, 1.04-1.60) when comparing participants who consumed 7 or more servings/wk (360 mL per serving) with those who consumed 1 serving/wk or less (Supplement [eTable 7]).

## Discussion

Our results suggest that the usual percentage of calories from added sugar among US adults increased from the late 1980s to 1999-2004 and decreased during 2005-2010. Most adults consumed more than 10% of their total calories from added sugar, and approximately 10% of adults consumed 25% or more of calories from added sugar in 2005-2010. Compared with those who consumed approximately 8.0% of calories from added sugar, participants who consumed approximately 17% to 21% (Q4) of calories from added sugar had a 38% higher risk of CVD mortality. This relative risk was more than double for those who consumed 21% or more (highest quintile) of calories from added sugar.

Major sources of added sugar in American adults' diet included sugar-sweetened beverages (37.1%), grain-based desserts (13.7%), fruit drinks (8.9%), dairy desserts (6.1%), and candy (5.8%).<sup>45</sup> One 360-mL can of regular soda contains about 35 g of sugar (140 calories) or 7% of total calories (based on 2000 kcal/d). There is no universally accepted guideline for added sugar consumption. The Institute of Medicine recommended no more than 25% calories from added sugar based on the NHANES III study of increased consumption of added sugar and reduced intake of macronutrients, especially at the level of more than 25%.<sup>3</sup> However, this recommendation did not consider health effects. The World Health Organization recommended less than 10% of calories from added sugar based on its assessment of higher consumption and adverse health outcomes.<sup>4</sup> With the evidence of higher added sugar consumption and adverse health outcomes accumulating, the American Heart Association recommended that total calories from added sugar should be less than 100 calories/d for most women and less than 150 calories/d for most men.<sup>5</sup> Our analysis suggests that participants who consumed greater than or equal to 10% but less than 25% of calories from added sugar, the level below the Institute of Medicine recommendation and above the World Health Organization/American Heart Association recommendation, had a 30% higher risk of CVD mortality; for those who consumed 25% or more of calories from added sugar, the relative risk was nearly tripled (fully adjusted HR, 2.75).

In our analysis, regular consumption of sugar-sweetened beverages ( $\geq 7$  servings/wk) was associated with increased risk of CVD mortality. Several observational studies<sup>22,46</sup> have suggested that higher intake of sugar-sweetened beverages is significantly associated with increased incidence of CVD, independent of other risk factors. In the present study, the positive association between added sugar intake and CVD mortality remained significant after adjusting for the conventional CVD risk factors, such as blood pressure and total serum cholesterol. The association might be mediated through additional biological pathways, although a single measure of these risk factors may not have captured the mediational effects. In addition, the observed association was consistent across age group, sex, race/ethnicity (except among non-Hispanic blacks), educational attainment, physical activity levels, HEI score, and BMI.

Epidemiologic studies<sup>5,47</sup> have suggested that higher consumption of added sugar is associated with increased consumption of total calories and unhealthy dietary patterns, which in turn might increase the risk of unhealthy outcomes, such as weight gain, type 2 diabetes mellitus, and CVD. Thus, added sugar intake may be a marker for unhealthy dietary patterns. However, when we adjusted for overall diet quality as reflected by HEI and its individual components, the results did not change appreciably, suggesting that the association between added sugar intake and CVD mortality was not explained by overall diet quality.

The biological mechanisms underlying the association between added sugar intake and CVD risk are not completely understood. Emerging evidence supports the hypothesis that excessive intake of added sugar might play a role through multiple pathways.<sup>14</sup> Animal studies<sup>48</sup> have suggested that high intake of refined sugars, independent of weight gain, was associated with the development of hypertension. A recent observational study<sup>20</sup> suggested that excessive consumption of sugar-sweetened beverages and sugar was independently associated with increased blood pressure. Excessive intake of sugar was also associated with increased *de novo* lipogenesis in the liver, hepatic triglyceride synthesis, and increased triglyceride levels, a known risk factor for CVD.<sup>5,49</sup> In one study,<sup>18</sup> regular intake of added sugar was significantly associated with increased triglyceride levels and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels. Another proposed pathway of the relationship between excessive sugar intake and increased CVD risk is its association with inflammation markers, which are key factors in the pathogenesis of CVD.<sup>14,50,51</sup> Several recent studies<sup>52,53</sup> have indicated an association between higher consumption of sugar-sweetened beverages and inflammatory markers. In addition, a recent study<sup>12</sup> suggested a significant interaction between genetic factors and sugar-sweetened beverage consumption in relation to BMI, in which higher consumption was associated with increased genetic effects of obesity. Another study<sup>54</sup> suggested that carrying a genetic variant in the *PNPLA3* gene might be susceptible to increased hepatic fat, which is associated with increased risk for CVD, when dietary sugar intake was high among Hispanic children. Further studies are needed to examine potential interactions between genetic susceptibility and added sugar intake in relation to CVD risk.

Our study has several strengths. First, the availability of data on added sugar intake from a series of nationally representative samples of US adults allowed us to examine trends of consumption. Second, we used a validated method to estimate the usual percentage of calories from added sugar. The use of the NCI method to estimate usual nutrient intake provided a more powerful way to assess nutrient-disease associations compared with the use of a single 24-hour dietary recall.<sup>34-36,38</sup> Finally, our study adjusted for a wide range of potential confounding variables.

There are also several limitations to our study. First, in NHANES III (1988-1994), approximately 8% ( $n = 962$ ) of the participants provided a second-day 24-hour dietary recall. However, these data were adequate to provide a robust estimate of usual intake of added sugar.<sup>31,34</sup> For later NHANES

years, more than 88% of the participants provided a second 24-hour recall. When we pooled 1999-2002 data (which had single 24-hour dietary recalls) with 2003-2004 data to estimate usual intake, our results were consistent when restricting analysis to NHANES 2003-2004 data (results not shown). Second, for the association analysis, added sugar intake was assessed at baseline and not updated during the follow-up period. The baseline exposure might not capture changes in intake over time. Third, although we adjusted for a comprehensive set of covariates in our multivariable models, the associations reported in our study may partially result from other unobserved confounding variables, from residual confounding, or by other dietary variables.<sup>55</sup> However, use of the HEI provided a comprehensive assessment of overall dietary pattern and should have significantly reduced the confounding effect of other dietary variables. Further adjusting the sodium intake did not alter the results. Fourth, the observed association between added sugar and CVD mortality was significant in other groups but not among non-Hispanic blacks, perhaps because of a limited number

of events in subgroups. Another possible explanation is that non-Hispanic blacks may be less susceptible to the metabolic effects of sugars, although this hypothesis needs to be further tested.<sup>12,54,56</sup> Finally, although observational studies are important in improving our understanding of nutrient-disease relationships, they should not be directly interpreted as evidence of causal relationships without considering other lines of evidence.<sup>57</sup>

## Conclusions

Our findings indicate that most US adults consume more added sugar than is recommended for a healthy diet. A higher percentage of calories from added sugar is associated with significantly increased risk of CVD mortality. In addition, regular consumption of sugar-sweetened beverages is associated with elevated CVD mortality. Our results support current recommendations to limit the intake of calories from added sugars in US diets.

### ARTICLE INFORMATION

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**Study concept and design:** Yang, Gregg, Hu.

**Acquisition of data:** Zhang.

**Analysis and interpretation of data:** Yang, Zhang, Flanders, Merritt, Hu.

**Drafting of the manuscript:** Yang.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Yang, Zhang, Flanders.

**Administrative, technical, or material support:** Gregg.

**Study supervision:** Yang, Hu.

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