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The association between sugary food and drinks intake and the risk of stroke mortality in the adventist health study-2

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A high consumption of added sugar has been associated with several cardiovascular risk factors, including obesity, type 2 diabetes mellitus and dyslipidemia. The main goal was to assess the association of sugary food and drink intake on the risk of stroke mortality. The Adventist Health Study-2 (AHS-2) is a prospective study with approximately 96,000 participants from the United States and Canada. Subjects were recruited from 2002 to 2007 at which time they completed a comprehensive food frequency questionnaire including intake of sugar added sweet foods and drinks. Subjects were followed with respect to National Death Index (NDI) mortality information through 2015. This is a low sugar consuming cohort where about 50% also adhere to a vegetarian dietary pattern. After applying exclusion criteria, the final analytical sample consisted of 53,482 study subjects. Cox Proportional hazard regression was used in the analyses adjusting for important demographic, lifestyle and medical variables. Four hundred and seventy two fatal strokes occurred during an average of 9.5 years or 509, 119 person-years of follow-up. Compared to the lowest quartile of sugary food intake (0 to 1.6 times/week), the hazard ratio of fatal stroke for the highest quartile (> 7 times/week) of sugary food intake was 0.86 (95% CI: 0.65 to 1.13), after adjusting for covariates. The hazard ratios did not change significantly when stratifying on gender and race. Consumption of added sugar was not associated with fatal stroke in this low sugar consuming population. Further research is needed in populations with higher intakes of sugar-sweetened foods and with diverse backgrounds and dietary patterns.

Key words: Diet, sugar, stroke, cardiovascular diseases.

INTRODUCTION

Production and consumption of refined sugar have increased dramatically during the twentieth century nationally and internationally, to the extent that added sugar is a main component in almost every meal (Cordain et al., 2005). On average, Americans derive about 13% of their daily caloric intake from added sugars,

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which is above the governmental recommended upper limit of 10% (2015–2020 Dietary Guidelines for Americans, 2015). Sugar-sweetened beverages (SSBs), desserts and snacks account for about 70% of the daily added sugar intake (2015–2020 Dietary Guidelines for Americans, 2015). The impact of carbohydrate intake in general has recently been assessed in the ARIC study (Seidelman et al., 2018) showing that high levels are associated with increased cardiovascular mortality. High carbohydrate intake is often associated with high sugar intake and the controversy regarding the role of sugar intake on health, particularly cardiovascular health, has been thoroughly discussed by Stanhope et al (2016). The associations between increased sugar consumption and well-established risk factors for stroke (Goldstein et al., 2011) such as obesity (Malik et al., 2013), diabetes type 2 (DM2), metabolic syndrome (Di Nicolantonio et al., 2015), dyslipidemia (Vos et al., 2017) and hypertension (Malik et al., 2014). They support the hypothesis that added sugar intake may increase the risk of both cardiovascular diseases in general (Yang et al., 2014; Atkins et al., 2016) and stroke specifically (Micha et al., 2017). Increased sugar consumption has been found to induce inflammation at the vascular level (Aeberli et al., 2011), thus increasing the risk of cardiovascular diseases (Levitan et al., 2004; Ridker et al., 1997). Stroke has a substantial impact on the economy and quality of life of its victims and is among the leading causes of death and disability worldwide (CDC, 2015a; WHO, 2015). In addition, African Americans in the U.S. have a higher intake of added sugar (CDC, 2015b) and they have a higher risk of stroke mortality compared with Whites (CDC, 2016). To date, only a few epidemiological studies have evaluated the relationship between sugar intake and risk of stroke and they are included in two recent meta-analyses (Narain et al., 2016; Bechthold et al., 2017). All of these explored this association based on sugar intake only in the form of SSBs. However, some of the studies did control for other sugar-containing foods (Bernstein et al., 2012; Eshak et al., 2012; Gardener et al., 2012; Pase et al., 2017). This research sought to explore the association between a more complete measure of added sugar consumption and stroke by using total intake of sugar sweetened foods and drinks as the exposure and stroke mortality as the outcome. The Adventist Health Study-2 (AHS-2), a large cohort study of a population with varied diet patterns, was used as the study population.

MATERIALS AND METHODS

Study population

The AHS-2 (AHS-2) is a prospective-cohort study. Recruitment (2002-2007) of subjects 30 years of age or older was done through all English-speaking Black (African- and Caribbean American) and white churches in the 50 US states as well as 5 provinces of Canada. No recruitment was done in other ethnic churches and thus only a very small fraction of Latinos and Asians were recruited. Trained pastors and “health coordinators” in each church promoted the study, using various means such as presentations, brochures, announcements and TV stations. Additionally, direct mails were sent to all church members who did not respond initially to the promotion. A more detailed description of the study and recruitment methods has been published elsewhere (Butler et al., 2008).

Study participants completed a comprehensive 48-page baseline questionnaire, which included demographic information, lifestyle characteristics, medical history, a female section, and a comprehensive and validated food frequency questionnaire (FFQ) (Jaceldo-Siegl et al., 2011). Approximately 96,000 participants had completed and returned the questionnaire by the end of recruitment in 2007.

The mean age at baseline was 58 years and 65.1% of the participants were females (Jaceldo-Siegl et al., 2011). In terms of race/ethnicity distribution, 65.3% were non-Hispanic White and 26.9% were African Americans/Blacks, with small proportions of other race/ethnicities. The study population has a wide variety of dietary patterns, with 53.2% of the participants being either vegans, lacto-ovo-, pesco- or semi-vegetarians and the rest classified as non-vegetarians (Butler et al., 2008). For the present analyses, subjects who at baseline reported prevalent stroke, transient ischemic attack (TIA), carotid artery surgery, diabetes mellitus, congestive heart failure, myocardial infarction, angina pectoris, coronary bypass surgery and stent surgery as well as hypercholesterolemia/regularly taking lipid-lowering medications were excluded. The History of hypertension was not excluded as this included a large number that would significantly reduce our analytic population. Instead, prevalent hypertension was included as a covariable. Also excluded were Canadian participants and subjects with invalid and/or unrealistic data values such as a daily caloric intake of < 500 or > 4500 kcal/day and body mass index (BMI) < 14 or > 60 kg/m^2. Thus, the final study population was 53,482 subjects (18,781 men and 34,701 women).

Assessment of sugary food intake

Consumption of sugary foods was assessed at baseline utilizing a validated semi-quantitative FFQ (Jaceldo-Siegl et al., 2011) which asked about intake of more than two hundred food items during the previous 12 months. Based on this FFQ the following drinks and food items to be included in the sugary foods category were identified: Sweetened drinks (regular Coke, Pepsi and other regular soft drinks and fruit punch) and “sweets and desserts” (doughnuts, cinnamon rolls, pastries, sweet pies, store-bought cookies, home-made cookies, cake, ice cream and milk shakes). In addition, sweet foods that were reported in two open ended questions in response to whether they used any other sweets and desserts not specifically identified in the multiple-choice questions were included. Total sugary food consumption was measured as frequency of intake (times/week) and in analysis was categorized into quartiles of intake.

Ascertainment of fatal stroke cases

Stroke mortality during follow-up was obtained by linking the AHS-2 database with the National Death Index (NDI) through 2015. Any mention of stroke on the death certificate was used to identify the outcome. The research also analyzed the data restricting the outcome to stroke as the underlying cause of death, but this severely reduced the number of cases so the main analyses were

completed using any mention of stroke on the death certificate. The International Classification of Diseases and Related Health Problems 10th Revision was used for coding of fatal stroke. The following codes were used: I61: Intracerebral hemorrhage, I62: Other non-traumatic intracranial hemorrhage, I63: Cerebral infarction and I64 Stroke, not specified as hemorrhage or infarction (ICD-10, 2018).

Potential covariates

Candidate variables were selected *a priori* based on literature review and availability in our database. The final analytic models include: age (time variable), sex (male, female), race (Black, non-Black), educational level (high school graduate or less, some college/Trade-school, college graduate or higher), BMI (14 to <25, 25 to <30, 30-60 kg/m^2), physical exercise (minutes/week) (0, > 0 to 60, > 60), alcohol consumption (current, past or never), smoking (never, ever). In addition, the following dichotomous variables (yes, no) were included: history of and/or current treatment of hypertension, history of cancer, regular aspirin intake in the last 5 years, hormone replacement therapy among menopausal women (ever, never). Also, continuous variables that included the intake of the following foods (grams/day): fruits and vegetables, meats, nuts, legumes, whole grains; and total energy intake (kilocalories/day).

Statistical analyses

Descriptive analyses comparing cases and non-cases, stratified to quartiles of sugary food intake were performed using Chi-square for categorical variables, and Student-t test and analysis of variance for continuous variables after log transformation to normalize the data. Cox proportional hazard regression analyses, with attained age as the time variable, was used to assess the relationship between sugary food consumption and stroke mortality controlling for selected covariates. Energy adjustment was done using the residual method (Willett et al., 1997). Frequency of intake was first used as a continuous variable in the analyses to assess linear relationships. For the individual models, frequencies of sugary food intake (times/week) were divided into quartiles (Q) of exposure: Q1:0-1.6; Q2:>1.6-3.5; Q3:>3.5-7.0; Q4:>7.0 times/week.

The basic model included age (time variable), sex, race and educational level. The final full model included the variables in the basic model plus BMI, physical exercise, alcohol consumption, smoking, history of hypertension or current antihypertensive treatment, regular aspirin intake in the last 5 years, hormone replacement therapy among menopausal women, history of cancer; intake of the following foods: fruits and vegetables, meats, nuts, legumes, whole grains; and total energy intake. Because high blood pressure and obesity may be considered intermediates in the relationship between sugar consumption and the risk of stroke mortality, sensitivity analyses were conducted by removing hypertension and BMI from the model one at a time. Another sensitivity analysis was performed where subjects were included with non-stroke comorbidities such as prevalence of DM2, congestive heart failure, myocardial infarction, angina pectoris, bypass surgery, stent surgery and hypercholesterolemia/regularly taking lipids lowering medications in the last 5 years. Finally, stratified analyses were performed based on gender and race. For the race-stratified analyses among the Blacks, reduced models were used due to low number of stroke deaths.

The proportional hazard assumption was tested using the Schoenfeld residuals method, survival curves, and testing the time interaction term in the model, and there was no evidence that the proportionality assumption was violated. A multiple imputation method was used to replace the small number of missing values, and particularly for dietary variables, a multiple guided imputation method was used if possible (Fraser and Yan, 2007). Five imputed datasets were used to estimate the hazard ratios and the correct standard errors, using Rubin formula (Rubin, 2004). The imputation procedure was done using R statistical package, version 2. 13. 1 (Willett et al., 1997) and the Hmisc, version 3. 14-0 package (Hu et al., 2014); while the survival analyses were conducted using SAS, 9.4 (SAS Institute Inc. Cary, NC).

RESULTS

During 9.5 years of follow-up (509,119 person-years), there were 472 fatal stroke cases (186 men and 286 women). Detailed baseline characteristics of the final analytic sample are described in Tables 1 and 2. Mean age was 55 years, about 65% were females and 27% were blacks. This was a well-educated population where more than 80% had completed some college or higher, and about 46% exercised more than 60 minutes per week and only about 18% regarded themselves as physically inactive. In spite of this, 33.3% were overweight and 20.5% were obese. Among the fatal stroke cases, 322 (68.2%) were non-specific, 28 ischemic, 71 hemorrhagic and 51 were characterized as “other non-traumatic intracranial hemorrhage”. Due to low numbers, these stroke sub-types during analyses were not differentiate, but used the sum of them as our outcome. The median frequency of sweet food intake in the upper quartile was 10.5 times/week, and the median intake of SSBs was once a week in the highest quartile, which is low compared to other populations (Eshak et al., 2012; Gardener et al., 2012; Larsson et al., 2014) (Figure 1). Compared to the subjects in the lowest quartile of sugary food intake, participants in the upper quartile were more likely to have lower educational level, exercise less, and have increased body weight. They were also more likely to be past smokers and current alcohol consumers. In terms of dietary habits, subjects who had higher intake of sugar were more likely to eat more meat, but less fruits, vegetables, whole grains, nuts and legumes. However, according to Table 2, the cases ate less meat and legumes, more fruit and vegetables, more nuts and more whole grains as compared to non-cases. However, Tables 1 and 2 are not age-adjusted, and cases were 23 years older than non-cases.

After adjusting for age, gender, race and educational level (basic model), no significant association was found between the risk of stroke mortality (any mention) and increased sugar intake (Table 3). The hazard ratio (HR), comparing the highest quartile of frequency of intake with the lowest was 0.90 (95% CI: 0.70-1.16). The estimates stayed virtually unchanged in the full multivariable model (HR=0.86, 95% CI: 0.65-1.13) (Table 3). Additionally, subgroup analyses according to gender and race (Blacks, non-Blacks) did not show a significant association between sugary food intake and fatal stroke risk.

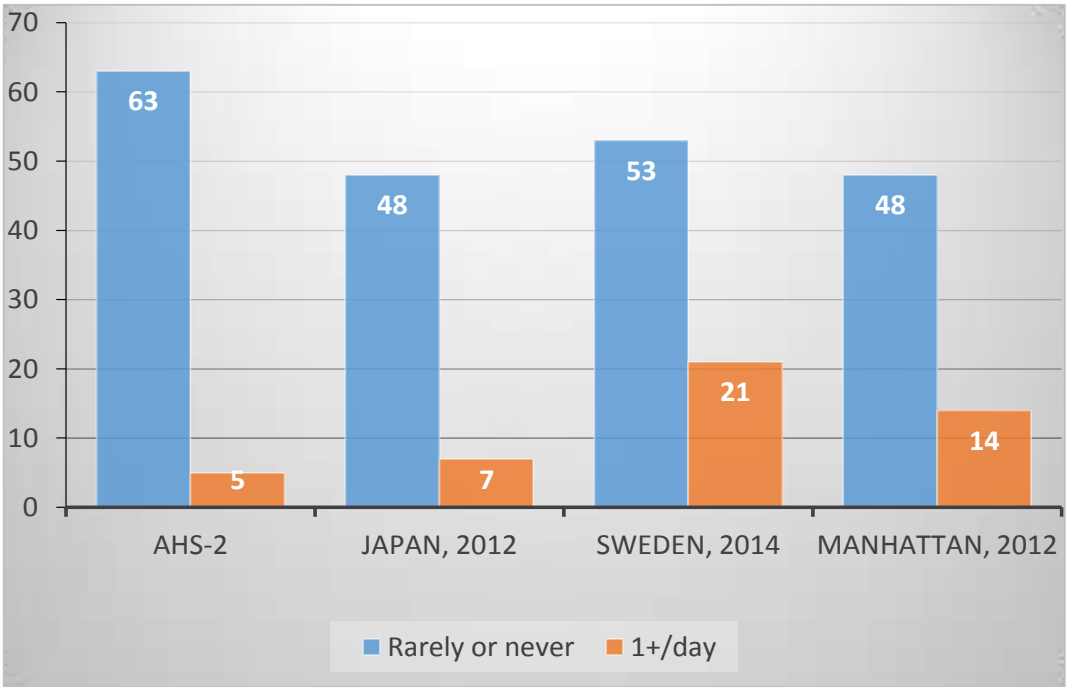

Figure 1. Percentage of populations with low or high levels of intake of sugar sweetened beverages (SSB).

Because smoking is a major risk factor for stroke and the majority (83%) of the AHS-2 subjects have never smoked, a sensitivity analysis limited to the never smoking group was performed. The estimates remained virtually unchanged compared to the estimates when including the rest of the population who were essentially all past smokers. Frequency of intake was also assessed as a continuous variable in the model after log-transformation and the HR was non-significant at 0.93 (95% CI: 0.82-1.04).

The sensitivity analyses with and without history of hypertension and BMI, respectively, in the model did not change the main effect associated with sweets intake. Likewise, when the non-stroke comorbidities were included, previously excluded, in the main analyses, the HRs stayed virtually the same as in the primary analyses.

DISCUSSION

No significant relationship between increased consumption of sugary foods and drinks and overall fatal stroke risk was found in our study. However, when stratified on race, the HR among the Blacks with in the highest quartile of sugary food intake was borderline protective with a HR=0.53 (p= 0.055). Unfortunately, our Black population was younger than the white subjects were and therefore there was only 72 cases and thus further studies among a larger and older population of Blacks are needed.

The AHS-2 is a population with relatively low sugar consumption with an average intake of 24 g/day (SD=16) of added sugar. This is low compared to the general US population who consume about 18.4 teaspoons of added sugar per day, equivalent to 77.3 grams (Bowman, 2017). There is information not only on SSB intake, but also on other foods with added sugar. Thus, to the best of our knowledge, this is the first study to assess a possible relationship between a more complete measure of added sugar consumption and risk of fatal stroke, whereas most other studies have assessed the effect of only SSB on stroke (Bernstein et al., 2012; Eshak et al., 2012; Gardener et al., 2012; Pase et al., 2017).

Results from studies on fatal stroke according to specific intakes of SSB intake are inconclusive. A cohort study in Japan (Eshak et al., 2012) found that, among women, the HR of incident ischemic stroke (fatal and non-fatal) was 1.83 (95% CI: 1.22-2.75) when comparing those who consumed SSBs every day with those who never or rarely consumed SSBs. For total stroke, however, results were not significant (HR=1.21, 95% CI: 0.88-1.68). Among men, there was a non-significant inverse association between consumption of SSBs and the risk of total and ischemic stroke with HRs at 0.76 (95% CI: 0.62-1.06) and 0.75 (95% CI: 0.53-1.03), respectively. The Framingham Heart Study Offspring

Table 1. Baseline characteristics of 53,482 AHS-2 Subjects according to sugary foods and drinks intake.

Categorical variable (%)	Sugary foods and drinks intake (frequency/week)					
	First quartile 0 to 1.6 n= 13,369	Second quartile 1.6 < to 3.5 N=13,371	Third quartile 3.5< to 7.0 N=13,372	Fourth quartile >7.0 N=13,370	Total N=53,482	P-value*
Gender						<0.01
Male	32.5	32.4	35.6	39.7	35.1	
Female	67.4	67.5	64.3	60.2	64.8	
Race						0.002
Black	27.9	26.5	25.9	26.3	26.7	
Non-Black	72.0	73.4	74.0	73.6	73.2	
Education						<0.01
High school	17.4	16.9	17.5	21.8	18.4	
Some college	38.8	38.4	39.0	40.0	39.0	
College or higher	43.7	44.6	43.4	38.1	42.4	
BMI						<0.01
<25	54.4	46.3	43.5	40.4	46.1	
25 to <30	29.6	33.7	34.3	35.3	33.2	
≥30	15.8	19.8	22.1	24.2	20.5	
Physical exercise (minutes/week)						<0.01
None	15.8	16.0	17.4	23.0	18.1	
0< to 60	31.3	36.5	37.6	37.9	35.8	
> 60	52.7	47.3	44.8	39.0	46.0	
Smoking						<0.01
Never	84.0	84.8	83.5	79.4	82.9	
Ever	15.9	15.2	16.4	20.5	17.0	
Alcohol intake						<0.01
Never	63.1	61.5	59.4	54.3	59.6	
Ever	29.2	28.6	29.7	32.5	30.0	
Current	7.6	9.7	10.8	13.1	10.3	
History of cancer						0.015
No	92.8	93.7	93.5	93.4	93.3	
Yes	7.1	6.2	6.4	6.5	6.6	
History of hypertension						<0.01
No	83.1	82.1	81.9	80.5	81.9	
Yes	16.9	17.8	18.0	19.4	18.0	
Aspirin use						<0.01
No	83.7	79.3	77.5	73.7	78.6	
Yes	16.2	20.6	22.4	26.2	21.3	

Table 1. Contd.

Hormonal replacement therapy among menopausal women					
<0.01					
No	53.4	49.6	48.1	46.5	49.5
Yes	46.5	50.4	51.8	53.4	50.4
Continuous Variables, Mean and standard deviation					
Age, years	55.9 (13.9)	54.6 (13.8)	54.8 (14.1)	55.3 (14.4)	<0.01
Total energy intake (kilocalorie/day)	1,974.2 (759.3)	1,821.2 (725.3)	1,866.7 (739.1)	2,006.8 (778.5)	<0.01
Fruits and vegetables (gram/day)	847.8 (548.5)	656.9 (412.5)	599.1 (386.3)	511.3 (341.9)	<0.01
Meat (gram/day)	18.7 (38.7)	24.5 (40.0)	29.2 (41.5)	38.9 (47.7)	<0.01
Nuts (gram/day)	22.8 (25.3)	17.6 (18.4)	16.6 (18.0)	14.6 (17.2)	<0.01
Legumes (gram/day)	63.6 (67.3)	52.2 (49.4)	49.2 (46.3)	43.1 (43.1)	<0.01
Whole grains (gram/day)	221.4 (161.6)	171.3 (135.3)	153.8 (122.2)	130.3 (112.6)	<0.01

*P-values associated with Chi-square for categorical variables and analysis of variance for continuous variables after log transformed across the quartiles of frequency of intake.

cohort found no significant association between SSBs and risk of total stroke incidence (HR=0.88, 95% CI: 0.43-1.78) when comparing SSB intake of >3 times/week to no intake (Pase et al., 2017). The Northern Manhattan Study also reported no association between consumption of SSBs and incident stroke (HR=1.00, 95% CI; 0.65-1.54) when comparing intake of SSB of ≥ 1 times/day to no intake (Gardener et al., 2012). Other studies have reported increased risk of stroke associated with high consumption of SSBs. The Health Professionals Follow-up Study and Nurses' Health Study found that consumption of ≥1 serving/day of SSBs increased the risk of total stroke (fatal and non-fatal) compared to those who did not drink SSBs, the pooled HR from the total cohort (men and women combined) was 1.16 (95% CI: 1.00-1.34). Among women the HR was 1.19 (95% CI: 1.00-1.42) whereas "a non-significant small increase" was found among the men (HR=1.08. 95% CI: 0.82-1.41) (Bernstein et al., 2012). Similarly, a study of Swedish men and women found that when comparing high SSBs intake of ≥2 servings/day with the reference of 0.1- < 0.5 servings/day, a significant increased risk of both total incident stroke (fatal and non-fatal) (19 %) and ischemic stroke (22%) was found, but no significant effect was apparent for hemorrhagic stroke (Larsson et al., 2014). Additionally, in a meta-analysis of four prospective studies with 259,176 subjects and 10,011 cases of incident stroke, the pooled relative risk (RR) for total stroke was 1.06 (95% CI: 0.97-1.15) for each serving/day increment in SSB intake. When comparing the highest level of SSB consumption to the lowest one, the summarized RR was 1.1 (95% CI: 1.00-1.20) for total stroke. The results were unstable when excluding one study at a time, and in a stratified analysis the summarized risk ratios were 1.16 (95% CI: 0.93-1.46) for ischemic stroke and 0.86 (95% CI: 0.71-1.04) for hemorrhagic stroke (Xi et al., 2015). A meta-analysis of four prospective studies reported pooled results suggesting a greater risk of stroke (RR=1.13, 95% CI: 1.02-1.24) with incremental (one serving/day) increase in SSB consumption (Narain et al., 2016). Another meta-analysis of seven prospective studies with 11,187 cases reported a RR for total stroke of 1.09 (95% CI: 1.01-1.18) comparing the highest SSB intake category with the lowest. Each additional daily 250 ml of SSB was positively associated with the risk of stroke (RR=1.07, 95% CI:1.02-1.12) (Bechthold et al., 2017). Also, when comparing data from NHANES 1999-2002 (n=8,104) and 2009-2012 (n=8,516), the reduction in stroke mortality was found to be associated with the reduction in SSB intake (Micha et al., 2017).

If intake of SSB is compared in thisstudy population with that of some of the other studies that have reported on the association between SSB and stroke risk, it is notably smaller. About 63% of the AHS-2 population never or rarely drink SSB and only 5% drink 1+ servings/day whereas the corresponding proportion of 1+ servings/day for the Swedish study (Larsson et al., 2014) and the Manhattan Study (Gardener et al., 2012) is 21 and 14%, respectively (Figure 1). Adventists are, in general, a health-conscious population (Butler et al., 2008), and compared to the average American, they tend to consume more fruits and vegetables, whole grains, legumes and nuts, but less meat, especially red meat (Fraser and Shavlik, 2001). It has been reported previously that subjects in the AHS-2 tend to become more vegetarian as they age (Martins et al., 2017) and in the AHS-1 it was discovered that subjects had the same chronic diseases as the general population, but tended to be diagnosed at an age about 10 years older than the

Table 2. Baseline characteristics of 53,482 AHS-2 subjects according to stroke cases and non-cases.

Categorical variable (%)	Non-cases N= 53,010 99.12%	Cases N=472 0.88%	Total N=53,482	P-value*
Gender				
Male	35.0	39.4	35.1	0.049
Female	64.9	60.5	64.8	
Race				<0.01
Black	26.8	15.2	26.7	
Non-Black	73.1	84.7	73.2	
Education				<0.01
High school	18.3	30.7	18.4	
Some college	39.1	36.2	39.0	
College or higher	42.5	33.0	42.4	
BMI				<0.01
<25	46.0	57.2	46.1	
25 to <30	33.3	28.3	33.2	
≥30	20.5	14.4	20.5	
Physical exercise (minutes/week)				<0.01
None	17.9	38.3	18.1	
0 < to 60	35.9	27.9	35.8	
> 60	46.1	33.6	46.0	
Smoking				0.157
Never	82.9	85.3	82.9	
Ever	17.0	14.6	17.0	
Alcohol intake				<0.01
Never	59.4	79.6	59.6	
Ever	30.1	16.7	30.0	
Current	10.4	16.7	10.3	
History of cancer				<0.01
No	93.4	83.2	93.3	
Yes	6.5	16.7	6.6	
History of hypertension				<0.01
No	82.0	67.5	81.9	
Yes	17.9	32.4	18.0	
Aspirin use				0.213
No	78.6	76.2	78.6	
Yes	21.3	23.7	21.3	

Table 2. Contd.

Hormonal replacement therapy among menopausal women				0.350
No	49.5	52.3	49.5	
Yes	50.4	47.6	50.4	
Sugary foods and drinks, frequency/wk				0.781
Quartile 1	24.9	26.4		
Quartile 2	25.0	23.7		
Quartile 3	25.0	23.9		
Quartile 4	24.9	25.8		
Continuous Variable, Mean and standard deviation				
Age, years	55.0 (13.9)	78.0 (10.8)		<0.01
Total energy intake (kilocalorie/day)	1916.7 (754.7)	1981.4 (748.5)		0.031
Fruits and vegetables (gram/day)	652.8 (446.0)	758.1 (509.8)		<0.01
Meat (gram/day)	27.9 (42.8)	16.9 (31.6)		<0.01
Nuts (gram/day)	17.8 (20.1)	23.6 (28.3)		<0.01
Legumes (gram/day)	52.1 (53.0)	43.7 (44.5)		<0.01
Whole grains (gram/day)	168.9 (138.1)	202.7 (157.6)		<0.01

*P-values associated with Chi-square for categorical variables and t-test for continuous variables after log transformed across the quartiles of sugary foods and drinks intake.

general population (Fraser, 2005). The study findings are in line with those previous reports showing an average age of 78 years for fatal stroke and that these cases tended to consume more plant-based foods than the young non-cases. This healthy diet could be a partial explanation for why the average age for fatal stroke is relatively high in this population. However, our HR did not change much even when adjusting for dietary factors. Since this population in general has a high intake of healthy foods and low meat intake, it is possible that a relatively small increase in sugary food intake does not represent an additional risk. High fruit and vegetable intake is associated with decreased risk of stroke (Hu et al., 2014) while increased consumption of red meat is associated with greater risk of total and ischemic stroke (Kaluza et al., 2012). Legumes and nuts have been found to reduce the risk of ischemic heart diseases, but the findings were inconclusive regarding stroke risk (Afshin et al., 2014). Thus, in essence, Adventists may consume foods containing adequate amounts of healthy nutrients such as antioxidants, which possess anti-inflammatory properties. Since inflammation is an essential component in the pathogenesis of cardiovascular diseases (Danesh et al., 2000; Pearson et al., 2003; Willerson and Ridker, 2004), it is reasonable to assume that a diet high in antioxidants may partially offset a potential harmful effect of sugar on fatal stroke risk (He et al., 2006; Schulze et al., 2005; Sørensen et al., 2005). The AHS-2 participants are virtually all non-smokers with about 83% never smokers, and cigarette smoking has been shown to induce an inflammatory response at the vascular level (Kangavari et al., 2004). Moreover, the AHS-2 cohort is characterized by low glycemic load (West-Write, 2018), and thus potentially lower stroke risk compared to subjects with food patterns with high glycemic load which are associated with increased stroke risk (Cai et al., 2015). It is, of course, also possible that a potential association between intake of sugar and fatal stroke is not a dose-response relationship, but a threshold effect, and that the low consumption of sugar in the AHS-2 population is below this threshold.

The present study has several strengths including the relatively large study sample size, its diversity in terms of race/ethnicities and educational status, and several well defined and validated food group intakes (Jaceldo-Siegl et al., 2011). In addition, there is a standardized method for registering mortality through linkage with the National Death Index. Nevertheless, the study is limited, first, by only having information on fatal stroke and not incident stroke. In addition, the case-fatality rate is greater for hemorrhagic stroke than for ischemic stroke (Andersen et al., 2009). In this study, most of the fatal strokes were coded as I64 (not specified as hemorrhage or infarction) and thus were unable to separate ischemic stroke from hemorrhagic stroke. This has probably attenuated the

Table 3. Hazard ratios (95% CIs) of total fatal stroke according to quartiles of sugary foods and drinks intake.

Variable	Sugary Foods and Drinks Intake (frequency/week)				
	First quartile 0 to 1.6	Second quartile 1.6 < to 3.5	Third quartile 3.5< to 7.0	Fourth quartile >7.0	P-trend
Person-years	126,785	127,489	127,738	127,107	
No. of Cases	125	112	113	122	
Model 1, HR (95% CI)	1.00 (reference)	0.97 (0.75- 1.26)	0.85 (0.63- 1.13)	0.90 (0.70-1.16)	0.28
Model 2, HR (95% CI)	1.00 (reference)	0.97 (0.75- 1.26)	0.83 (0.61 - 1.11)	0.86 (0.65-1.13)	0.17
Men					
Person-years	40,824	41,223	45,042	50,252	
No. of Cases	48	40	40	58	
Model 3, HR (95% CI)	1.00 (reference)	0.92 (0.60- 1.42)	0.85 (0.54- 1.33)	0.99 (0.67- 1.47)	0.92
Model 4, HR (95% CI)	1.00 (reference)	0.91 (0.58- 1.40)	0.82 (0.52- 1.30)	0.93 (0.60-1.43)	0.67
Women					
Person-years	85,962	86,266	82,697	76,854	
No. of Cases	77	72	73	64	
Model 3, HR (95% CI)	1.00 (reference)	1.01(0.73- 1.40)	0.85 (0.58- 1.25)	0.85 (0.61-1.18)	0.21
Model 4, HR (95% CI)	1.00 (reference)	1.02 (0.74- 1.42)	0.85 (0.57- 1.25)	0.82 (0.57-1.17)	0.18
Non-Blacks					
Person-years	91,669	93,851	94,883	93,660	
No. of Cases	104	91	94	111	
Model 3, HR (95% CI)	1.00 (reference)	0.95 (0.71- 1.27)	0.87 (0.65- 1.16)	0.95 (0.72- 1.26)	0.63
Model 4, HR (95% CI)	1.00 (reference)	0.97 (0.72- 1.30)	0.86 (0.64- 1.17)	0.94 (0.69-1.27)	0.54
Blacks					
Person-years	35,117	33,638	32,855	33,446	
No. of Cases	21	21	19	11	
Model 3, HR (95% CI)	1.00 (reference)	1.09 (0.55- 2.18)	0.75 (0.29- 1.90)	0.59 (0.29-1.20)	0.11
Model 5, HR (95% CI)	1.00 (reference)	1.02 (0.51- 2.07)	0.67 (0.27- 1.69)	0.53 (0.26-1.09)	0.055

Model 1: age, gender, race, and education
Model 2: Model 1 + BMI, physical exercise, alcohol intake, smoking, history of cancer, history of hypertension, aspirin intake in the last 5 years, hormonal replacement therapy among menopausal women, fruits and vegetable, meat, nuts, legumes, whole grains and total energy intake (kilocalorie/day).
Model 3 (subgroup analysis: men or women, Blacks or non-Black): age and education (gender or race depending on subgroup)
Model 4: Model 3 + BMI, physical exercise, alcohol intake, smoking, history of cancer, history of hypertension, aspirin intake in the last 5 years, hormonal replacement therapy among menopausal women (not in the male model), fruits and vegetable, meat, nuts, legumes, whole grains and total energy intake (kilocalorie/day).
Model 5: (subgroup analyses among Blacks): age, gender, BMI, and physical exercise.

estimates since earlier findings indicate that sugar intake may be a risk factor mostly for ischemic stroke (Bernstein et al., 2012; Eshak et al., 2012; Gardener et al., 2012; Pase et al., 2017). In addition, there are no information about atrial fibrillation and the family history of cardiovascular diseases, two important risk factors for stroke. The fact that our population overall had low sugary food intake also limits our ability to make conclusions regarding the effects of higher levels of sugar intake. It is possible that a detrimental effect of sugar intake is only evident at higher levels of intake.

Conclusions

In conclusion, the present study did not find any association between sugary food intake and fatal stroke when explored in this population with low sugar intake in the context of general healthy dietary pattern and lifestyle habits. It is possible that there is a threshold effect and

that sugar is only detrimental for stroke when taken in amounts higher than this threshold. It is also possible that a moderate intake of added sugar is not a risk factor for stroke in populations with a generally healthy lifestyle. Further studies are, therefore needed in populations with higher intake of sugar. Furthermore, additional studies using incident stroke, especially incident ischemic stroke are necessary. Lastly, the relationship between sugar intake and the risk of stroke needs further in-depth research, to explore the potential role of other dietary factors in modifying a possible effect of sugar intake on stroke risk.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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