



Published in final edited form as:

Circulation. 2019 April 30; 139(18): 2113–2125. doi:10.1161/CIRCULATIONAHA.118.037401.

Long-term Consumption of Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Mortality in US adults

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Abstract

Background: Whether consumption of sugar sweetened beverages (SSBs) or artificially sweetened beverages (ASBs) is associated with risk of mortality is of public health interest.

Methods: We examined associations between consumption of SSBs and ASBs with risk of total and cause-specific mortality among 37,716 men from the Health Professional's Follow-up study (from 1986-2014) and 80,647 women from the Nurses' Health study (from 1980-2014) who were free from chronic diseases at baseline. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Results: We documented 36,436 deaths (7,896 CVD and 12,380 cancer deaths) during 3,415,564 person-years of follow-up. After adjusting for major diet and lifestyle factors, consumption of SSBs was associated with a higher risk of total mortality; pooled HRs (95% CIs) across categories (<1/month, 1-4/month, 2-6/week, 1-2/day and ≥2/day) were 1.00 (reference), 1.01 (0.98, 1.04), 1.06 (1.03, 1.09), 1.14 (1.09, 1.19), and 1.21 (1.13, 1.28; p-trend <0.0001). The association was observed for CVD mortality [HR comparing extreme categories was 1.31 (95% CI: 1.15, 1.50), p-trend <0.0001] and cancer mortality [1.16 (1.04, 1.29), p-trend =0.0004]. ASBs were associated with total and CVD mortality in the highest intake category only; pooled HR's (95% CI) across

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Conflict of Interest Disclosures: WCW and VSM are on a pro bono retainer for expert support for the Center for Science in the Public Interest in litigation related to sugar sweetened beverages and have served as consultants for the City of San Francisco for a case related to health warning labels on soda. None of the other authors have financial or personal conflicts of interest to disclose that are related to the contents of this paper.

categories were 1.00 (reference), 0.96 (0.93, 0.99), 0.97 (0.95, 1.00), 0.98 (0.94, 1.03) and 1.04 (1.02, 1.12) (p-trend 0.01) for total mortality and 1.00 (reference), 0.93 (0.87, 1.00), 0.95 (0.89, 1.00), 1.02 (0.94, 1.12) and 1.13 (1.02, 1.25) (p-trend 0.02) for CVD mortality. In cohort-specific analysis, ASBs were associated with mortality in NHS but not in HPFS (p-interaction, 0.01). ASBs were not associated with cancer mortality in either cohort.

Conclusions: Consumption of SSBs was positively associated with mortality primarily through CVD mortality and showed a graded association with dose. The positive association between high intake levels of ASBs and total and CVD mortality observed among women requires further confirmation.

Keywords

Sugar sweetened beverages; low calorie beverages; artificially sweetened beverages; all-cause death; cardiovascular death

Introduction

Sugar sweetened beverages (SSBs) are the single largest source of added sugar in the US diet^{1, 2}. They include the full spectrum of carbonated and non-carbonated soft drinks, fruit drinks and sports drinks that contain added caloric sweeteners such as high fructose corn syrup (HFCS), sucrose, or fruit juice concentrates. Although consumption of SSBs in the US has decreased in the past decade³, national survey data show a slight rebound in consumption in recent years among adults in most age groups with an average intake of 145 kcal per day, equivalent to 6.5% of energy. Among younger adults, SSB contributed 9.3% of daily calories in men and 8.2% in women^{4, 5}. These intake levels nearly exceed dietary recommendations for consuming no more than 10% of total energy from all added sugar⁶. In other parts of the world, particularly developing countries, intake of SSBs is rising dramatically due to widespread urbanization and beverage marketing⁷.

In epidemiological studies, intake of SSBs has been associated with weight gain⁸ and higher risk of type 2 diabetes⁹, coronary heart disease^{10, 11} and stroke¹². To date, few studies have examined the association between SSB intake and mortality. A prospective analysis of National Health and Nutrition Examination Survey (NHANES) data found positive associations between baseline intakes of added sugar and SSBs with CVD mortality¹³. In contrast, results from a cohort of Chinese adults in Singapore with very low intake levels found no significant association between SSBs and mortality¹⁴, while another study among elderly participants in the US found a higher risk of death associated with consumption of artificially sweetened beverages (ASBs) but not SSBs¹⁵. However, the latter finding may be due to reverse causation, switching from SSBs to ASBs because of underlying conditions, as illustrated in some studies of ASBs and risks of diabetes and heart disease^{11, 16}. ASBs are often suggested as alternatives to SSBs and intake levels of ASBs have increased in the US¹⁷, but little is known about their long-term health effects. Thus, we investigated the associations between SSBs and ASBs with total and cause-specific mortality in two large cohorts of US men and women who were middle-aged at baseline with repeated measurements of diet over 28–34 years.

Methods

The data, analytical methods, and study materials will be made available to other researchers from the corresponding authors on reasonable request for purposes of reproducing the results or replicating the procedure.

Study Population

Our analysis was conducted in two ongoing prospective cohort studies: The Nurses' Health Study (NHS), which was initiated in 1976 and included 121,700 women, aged 30–55 years at entry, and the Health Professionals Follow up Study (HPFS), which began in 1986 among 51,529 men aged 40–75 years. For both cohorts, mailed questionnaires were administered biennially to assess lifestyle factors and health status, with a follow-up rate exceeding 90% for each 2-year cycle. Diet was assessed using a validated self-administered food frequency questionnaire (FFQ) every 4 years. Dietary data were first collected in 1980 in the NHS and in 1986 for the HPFS; we used these years as baseline. We excluded individuals with a history of diabetes, cardiovascular disease (CVD) or cancer at baseline and those who left >70 items blank on the baseline FFQ, had missing data about SSB intake or reported implausible intakes of total energy (< 500 or >3500 kcal/d for women and <800 or >4200 kcal/day for men). After exclusions, a total of 80,647 women and 37,716 men remained for the analysis. Protocols for these studies were approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health and participants gave informed consent.

Assessment of Beverage Intake

In 1980, intake of SSB and ASB was assessed among NHS participants using a 61-item FFQ designed to assess usual diet over the previous year. A similar but expanded FFQ with 131–166 items, was administered in subsequent questionnaire cycles to NHS (1984, 1986, 1990, 1994, 1998, 2002, 2006 and 2010) and HPFS (1986, 1990, 1994, 1998, 2002, 2006 and 2010) participants. On each FFQ we asked participants how often, on average they consumed a standard portion of foods and beverages (one standard glass, bottle or can), using 9 possible responses ranging from “never or less than once per month” to “6 or more times per day. Nutrient and energy intakes were calculated by multiplying the frequency of consumption of each unit of food and beverage by nutrient and energy contents and summing across all items. Total SSBs were defined as caffeinated colas, caffeine-free colas, other (i.e. non-cola) carbonated sugar-sweetened beverages, and noncarbonated sugar-sweetened beverages (fruit punches, lemonades, or other fruit drinks). Fruit juice was not considered a SSB. ASBs were defined as caffeinated, caffeine-free, and noncarbonated low-calorie or diet beverages. The reproducibility and validity of these FFQs have been described elsewhere^{18, 19}. Briefly, the correlation coefficients between the FFQ and multiple dietary records were 0.84 for colas, 0.36 for other carbonated soft drinks, and 0.56 for noncarbonated sweetened beverages among NHS participants¹⁹. Similar values were found in the HPFS¹⁸. SSB consumption has also been associated with biomarkers including higher plasma triglycerides and inflammatory cytokines and lower high density lipoprotein and leptin in our cohorts, providing further evidence of the validity of our measurements^{11, 20}.

Ascertainment of Death

Deaths were identified from state vital statistics records and the National Death Index or by reports from next of kin or the postal authorities. More than 97% of deaths were identified for these cohorts²¹. Cause of death was determined by physician review of medical records, autopsy reports or death certificates. We used the *International Classification of Diseases, Eighth Revision (ICD-8)* in NHS and *ICD-9* in HPFS, which was widely used at the time the cohorts began, to distinguish between deaths due to CVD (ICD codes 390 to 458 in the NHS and 390–459 in the HPFS) and cancer (ICD codes 140 to 207 in the NHS and 140 to 208 in the HPFS). For breast cancer mortality we used ICD code 174, for lung cancer mortality ICD code 162 and for colon cancer mortality ICD codes 153 and 154.

Assessment of Covariates

For both cohorts, information on lifestyle factors and medical history, including age, body weight, smoking status, physical activity, medication and supplement use, disease diagnoses and family history of chronic diseases was obtained from biennial questionnaires. Body mass index (BMI) (weight in kilograms divided by height in meters squared) was calculated from body weight reported on each follow-up questionnaire and height reported at study initiation. Information on dietary factors was obtained from updated FFQs. A modified Alternate Healthy Eating Index (AHEI) score, with SSBs removed was used as an indicator of overall diet quality. This score was calculated based on 10 foods and nutrients that are predictive of chronic disease risk including fruit, vegetables, nuts and legumes, red and processed meat, whole grains, alcohol, sodium, trans fat, long chain omega-3 and other polyunsaturated fats.²² A higher score denotes greater adherence to the AHEI and better diet quality.

Statistical Analysis

Age-stratified Cox proportional hazards regression was used to model the associations between SSBs and ASBs with total and cause-specific mortality separately for each cohort. Person-time was calculated for each participant from baseline until the end of follow-up (June 30, 2014 for the NHS and January 31, 2014 for the HPFS), or death, whichever occurred first. Beverage intake was categorized by frequency: <1/mo (reference), 1–4/mo, 2–6/wk, 1–<2/d, and 2/d, and linear trends were evaluated using the Wald test on a continuous variable representing median intakes of each category. In secondary analysis, we collapsed the first two categories of intake since the majority of participants consumed <1 serving per week. We also assessed ASB using the following categories to reflect the greater frequency of intake, which was not possible for SSB because of the lower intake levels: <1/mo (reference), 1–4/mo, 2–6/wk, 1–<2/d, 2–<4/d and 4/d. Given the long durations of follow-up in our cohorts and because intake levels of SSBs and ASBs have changed over time, we used dietary intake reported at the beginning of each FFQ cycle, which was updated by repeated FFQs throughout follow-up²³. In secondary analysis, to better represent long-term average diet, we repeated the analysis using cumulative averages of dietary data that were created using repeated measures from the FFQs (calculated by taking the mean intake from all FFQs up to the beginning of a follow up interval). We also repeated the analysis using baseline dietary intake and with an 8-year lag, whereby exposures were

evaluated in relation to outcomes 8 years later. Missing values were replaced with those from the preceding FFQ cycle. Multivariate models were adjusted for age and race (white or nonwhite) and time-varying covariates including smoking status (never, past or current [1–14, 15–24 or ≥25 cigarettes per day]), postmenopausal status and hormone use (NHS only), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15 g/d for NHS and 0, 0.1–4.9, 5.0–29.9 or ≥30 g/d for HPFS), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 or ≥27.0 hours of metabolic equivalent tasks (METs) per week), multivitamin use (yes or no), aspirin use (yes or no), family history of diabetes mellitus, myocardial infarction, or cancer, baseline history of hypertension or hypercholesterolemia and intakes of total energy, whole grains, fruit, vegetables, and red and processed meat in quintiles. In secondary analysis, we replaced individual foods in the model with the AHEI score (in quintiles). All models were mutually adjusted for SSB and ASB in quintiles. BMI (<23.0, 23.0–24.9, 25.0–29.9, 30.0–34.9 or ≥35 kg/m²) was subsequently added to the models as it may partly mediate the association between SSB/ASB and risk of death.

To minimize potential reverse causation resulting from changes in SSB and ASB intakes because of illness or attempt to lose weight, we applied the lifelong maximum BMI by age-at-risk approach²⁴, whereby the maximum value of BMI reported prior to outcome assessment is used for risk prediction. For example, the maximum value of BMI at age 18 and BMI reported in 1980 was used to predict mortality between 1980 and 1982, and the maximum value of BMI at age 18, BMI reported in 1980 and BMI reported in 1982 was used to predict mortality between 1982–1984 and so forth. To evaluate whether occurrence of an intermediate chronic condition may mediate associations, we also adjusted for hypertension, hypercholesterolemia, diabetes mellitus, CHD, stroke and cancer in sensitivity analysis. Because diagnosis of an intermediate disease might lead to changes in diet or recall bias, we stopped updating dietary variables when participants reported having diabetes mellitus, stroke, CHD or cancer. In sensitivity analysis, we repeated the analysis without stopping updating diet. Stratified analyses and potential interaction with age (<65 y vs. ≥65 y), BMI (<25 or ≥25 kg/m²), physical activity (based on median), and diet quality as assessed by the AHEI (based on median) was evaluated using the Wald test on cross-product terms based on beverage intake (continuous variable) and the stratification variables.

We also evaluated the association of substituting 1 serving per day of SSB with an equivalent amount of ASB by including both as continuous variables simultaneously in the multivariable model. The difference between beta coefficients and variance and the covariance were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the substitution association. All statistical tests were two-sided with a p-value <0.05 and performed using SAS version 9.2 for UNIX (SAS Institute, Cary, NC). Pooled HR's were obtained by combining data from both cohorts to increase statistical power and obtain summary estimates.

Results

During 34 years of follow-up in the NHS, we documented 23,432 deaths (4,139 CVD and 8,318 cancer) and during 28 years of follow-up in the HPFS we documented 13,004 deaths (3,757 CVD and 4,062 cancer). Mean consumption of SSBs decreased in both cohorts over

the course of follow-up, while intake of ASBs increased initially and then decreased (Supplemental Figure 1). Intakes of SSBs and ASBs were slightly inversely correlated in the NHS ($r=-0.06$, $p<0.001$) and HPFS ($r=-0.16$, $p<0.001$). Characteristics of participants according to frequency of SSB and ASB intake are shown in Table 1. Given the long duration of follow-up, the data shown are from 1994, which is the approximate mid-point of follow-up. Men and women with higher intakes of SSBs tended to be younger, less physically active, less likely to take a multivitamin and more likely to smoke compared to those with lower intakes (Table 1). SSB consumption was also associated with a higher intake of total energy, red and processed meat and glycemic load and with a lower intake of whole grains and vegetables. Individuals with higher intakes of ASBs were also more likely to be younger than infrequent consumers and to have hypertension, a greater BMI and tendency to be overweight. ASB intake was associated with a lower glycemic load.

After adjusting for age and ASB consumption, intake of SSBs was associated with an increased risk for total mortality in both cohorts (Table 2). Compared to those who consumed SSBs less than once per month, women who consumed 2 servings of SSBs per day had a 63% higher risk of death (HR: 1.63; 95% CI: 1.52, 1.75) and for men the estimate was 29% (HR: 1.29; 95% CI: 1.15, 1.44). The pooled HR (95% CI) was 1.52 (1.43, 1.61). After adjusting for demographic and lifestyle factors (smoking, alcohol intake, postmenopausal hormone use (NHS), physical activity, family history of diabetes, family history of myocardial infarction, family history of cancer, multivitamin use, ethnicity, aspirin use), the association was attenuated (HR: 1.30; 95% CI: 1.22, 1.38). Additional adjustment for baseline hypertension and hypercholesterolemia, intakes of whole grains, fruit, vegetables, red and processed meat, total energy and BMI further attenuated the association (HR was 1.21 (95% CI: 1.13, 1.28; p-trend: <0.001). BMI was included in the multivariate model since results were similar if BMI was removed. Each serving per day increment in SSB was associated with a 7% higher risk of death (HR: 1.07; 95% CI: 1.05, 1.09). An interaction with sex was observed with stronger associations in the NHS than HPFS (p-interaction, 0.02). Associations were similar for different types of SSBs with a serving per day increment in risk of 7% (95% CI: 4%, 10%) for cola, 8% (3%, 13%) for non-cola carbonated beverages and 7% (4%, 10%) for non-carbonated beverages (Supplemental Table 1). After adjusting for incidence of intermediate conditions including, hypertension, hypercholesterolemia, type 2 diabetes, CHD and stroke during follow-up, the association between SSBs and mortality was attenuated but still statistically significant: (HR for one serving/day: 1.05; 95% CI: 1.03, 1.07) (not shown).

SSB intake was also associated with increased risk for CVD mortality, which was more pronounced than for cancer mortality (Table 2). In the pooled, fully adjusted analysis, compared to infrequent consumers, those who consumed 2 servings of SSBs per day had a 31% (HR: 1.31; 95% CI: 1.15, 1.50; p-trend, <0.0001) higher risk of death from CVD. Estimates were greater in the NHS compared to HPFS but no interaction with sex was observed (p-interaction, 0.70). Each serving per day increment of SSBs was associated with a 10% higher risk of CVD death (HR: 1.10; 95% CI: 1.06, 1.14). Modest associations between SSB intake and cancer mortality were observed among both cohorts [HR (95% CI): 1.16 (1.04, 1.29); p-trend: 0.0004, comparing extreme categories from the pooled analysis]. Among women, there was a positive association between intake of SSB and breast

cancer mortality [HR (95 % CI): 1.34 (1.00, 1.80); p-trend: 0.02, comparing extreme categories] and a borderline positive association was observed between SSB intake and colon cancer in both cohorts (Table 3).

ASB intake was positively associated with risk of total and CVD mortality in the highest category in the NHS: HRs (95% CI) across categories (<1/month, 1 to 4/month, 2 to 6/week, 1 to <2/day and 2/day) were 1.00 (reference), 0.96 (0.93, 1.00), 0.94 (0.91, 0.98), 0.97 (0.93, 1.02), and 1.10 (1.04, 1.16), p-trend= 0.01 for total mortality and 1.00 (reference), 0.90 (0.82, 0.99), 0.89 (0.82, 0.98), 0.95 (0.84, 1.07), and 1.15 (1.01, 1.31), p-trend= 0.08 for CVD mortality (Table 4). After adjusting for incidence of intermediate conditions (hypertension, hypercholesterolemia, type 2 diabetes, CHD and stroke) during follow-up, the association between ASBs and total mortality in NHS was attenuated: (HR comparing extreme categories: 1.00; 95% CI: 0.94, 1.06) (not shown). No associations were observed between ASB and total and CVD mortality in HPFS. An interaction with sex was observed for total mortality (p-interaction, 0.01) but not CVD mortality (p-interaction, 0.14). Intake of ASB's was not associated with cancer mortality in either cohort (Tables 3 and 4). When examining higher intake levels, we observed positive associations between ASB and total and CVD mortality at intakes 4 servings per day in the NHS (Supplemental table 2). HRs (95% CIs) across categories (<1/month, 1 to 4/month, 2 to 6/week, 1 to <2/day, 2 to <4/day and 4/day) were 1.00 (reference), 0.96 (0.93, 1.00), 0.94 (0.91, 0.98), 0.97 (0.93, 1.02), 1.06 (1.00, 1.13), and 1.30 (1.15, 1.46), p trend =0.0001 for total mortality and 1.00 (reference), 0.90 (0.82, 0.99), 0.89 (0.82, 0.98), 0.95 (0.84, 1.07), 1.09 (0.95, 1.26), and 1.43 (1.10, 1.87), p trend =0.02 for CVD mortality. No associations were observed in HPFS.

We found significant positive associations between SSB and mortality in all categories of diet quality, physical activity, BMI and age (p-interaction > 0.10 for all) (Figure 1). For the association between ASB and mortality, positive associations were observed among some subgroups (high AHEI score, high physical activity level, BMI 25 and age 65 years or older) but not in others (low AHEI score, low physical activity level, BMI <25 and younger than 65 years) in the pooled analysis. However, significant interactions were observed only for BMI and physical activity (p-interaction, <0.05) (figure 1).

We estimated that replacing 1 serving per day of SSB with 1 serving per day of ASB was associated with a 4% lower risk of total mortality [HR (95 % CI): 0.96 (0.94, 0.98)], 5% lower risk of CVD mortality [HR (95 % CI): 0.95 (0.90, 0.99)] and 4 % lower risk of cancer mortality [HR (95 % CI): 0.96 (0.93, 1.00)].

In the analysis without stopping updating diet with occurrence of chronic diseases, associations with SSB were similar for total mortality, attenuated for CVD mortality and strengthened for cancer mortality (Supplemental Table 3). When using cumulative averages, associations with SSB were similar for total and CVD mortality and attenuated for cancer mortality (supplemental table 3). Associations were attenuated when baseline data and an 8-year lag were used but similar when AHEI was used instead of individual foods in the models (supplemental table 3.) For ASBs, associations for the 3 outcomes were attenuated (with positive associations for total and CVD mortality dissipated) in all sensitivity analyses except for when AHEI was used in the models instead of individual foods, which resulted in

similar estimates to those reported in the primary analysis (supplemental table 3). For both SSBs and ASBs, associations for all outcomes were similar when 4 instead of 5 categories of intake were used (Supplemental Table 4).

Discussion

In these two large prospective cohorts of US men and women, we found a positive graded association with dose between intake of SSBs and risk of mortality after adjusting for diet and lifestyle factors. This association was driven by CVD mortality with a stronger association observed among women compared to men, although no significant interaction with sex was observed. We also found a modest positive association between SSB intake and risk of cancer mortality. Intake of ASBs was positively associated with total and CVD mortality at high intake levels (at least 4 servings per day) and associations were statistically significant only among women. ASB intake was not associated with cancer mortality. Substituting 1 serv/d of SSB with ASB was associated with modest reductions in total and cause-specific mortality.

SSBs are the single largest source of added sugar in the US diet^{1, 2}. A typical 12 oz. serving of soda contains 140–150 calories and 35.0–37.5 g of sugar. Positive associations between SSB intake and weight gain,^{8, 25} risk of diabetes⁹ and CHD^{10, 11} have attracted much scientific interest, but little is known about whether intake of these beverages impacts risk of mortality. However, this may be expected given their associations with the above conditions. In a previous prospective analysis of NHANES data using baseline intake levels, greater intake of added sugar and SSBs was associated with a higher risk of CVD mortality after a median of 14.6 years of follow-up¹³. Our study, with longer follow-up, a larger sample size and repeated measurements of diet confirm these findings. In contrast to our study, no association was observed between SSB intake and risk of mortality in the Singapore Chinese Health Study¹⁴ or in a cohort of elderly adults¹⁵. However, both of these studies were much smaller and used only baseline intake of SSB with very low intake levels.

Intake of SSBs may contribute to risk of mortality through inducing cardiometabolic and chronic disease risk. In our cohorts, SSB intake has been associated with weight gain²⁶ and higher risk of hypertension²⁷, diabetes^{16, 28}, CHD^{10, 11} and stroke¹². This is supported by our observation that estimates for SSB were partly attenuated after adjusting for intermediate chronic conditions. Excess adiposity is an important risk factor for these conditions as well as premature death^{29, 30}. However, in our analysis adjusting for BMI did not alter the estimates, suggesting that the observed associations may be independent of this factor. Because of the increasing age of participants in our cohorts, it is possible that BMI may not accurately reflect adiposity. We observed stronger associations with total and CVD mortality among women compared to men. Whether there is a biological basis for this difference is not clear but it could be due to metabolic differences between men and women. Consistent with some studies^{31, 32}, we found a modest positive association between SSB intake and cancer mortality. Of note, this outcome included deaths from all cancers. However, our analysis of cause-specific cancer mortality suggests that the association between SSB and total cancer mortality is likely driven by diet-related cancers including breast and to a lesser extent colon. The evidence linking SSB to cancer is mixed and may depend on the etiology

of specific cancer types. More research exploring the association between SSB and cancer warrants further study.

Our findings on ASBs and mortality are consistent with our previous studies of diabetes¹⁶ and CHD^{10, 11}, which found attenuated associations after taking analytic steps to reduce reverse causation and support RCT's that have found weight control benefits of substituting diet soda for regular soda at moderate intakes of 1–2 per day^{33, 34}. In our analysis, greater intake of ASB was positively associated with BMI and hypertension, suggestive of reverse causation. After adjusting for these and other factors, there was no association between ASB intake and mortality in the HPFS and estimates were attenuated in the NHS and significant only at intakes of 4 or more per day. The borderline inverse association observed with total and CVD mortality at moderate ASB intake levels is likely due to residual confounding by other potentially healthful lifestyle choices and was observed primarily among NHS participants. Given our findings, it would be of interest to explore higher levels of ASB intake on cardiometabolic outcomes in future studies. Of note, the positive association between ASB and mortality was found only among those who were overweight or had high levels of physical activity in stratified analysis, further supporting reverse causation.

Some research has suggested that ASBs may increase body weight and contribute to cardiometabolic risk despite containing few to no calories because of the intense sweetness of artificial sweeteners, which may habituate towards a preference for sweets or stimulate a cephalic inulin response and more recently through alterations in gut microflora linked to insulin resistance³⁵. However, these mechanisms are not well understood and reverse causation and residual confounding may partly explain the positive associations observed with cardiometabolic outcomes in some cohort studies as well as in our study³⁶. It should also be noted that there are no dietary interventions involving chronic ASB exposure in which ASB induced a body weight increase relative to sugar, water or habitual diet³⁷. Although we did not observe an association between ASBs and cancer, a previous study in our cohorts found that ASBs were associated with higher risk for non-Hodgkin lymphoma and multiple myeloma in men but not in women, and with leukemia when men and women were combined³⁸. While the potential carcinogenicity of aspartame, the primary artificial sweetener in ASBs is biologically plausible, the findings could also be due to chance.

Strengths of our study include the large sample size, long-term and high rates of follow-up, detailed and repeated measurements of diet and lifestyle and numerous sensitivity analyses that support the robustness of the results. As with any observational study, the possibility of residual confounding cannot be ruled out despite adjusting for numerous diet and lifestyle factors in our analysis. Higher SSB intake could be a marker of a globally unhealthy diet and incomplete adjustment for various factors could lead to an overestimation of the association between SSBs and mortality. When we adjusted for individual foods, and for AHEI as a marker of diet quality in sensitivity analysis, associations were attenuated but remained significant, suggesting some positive confounding in the unadjusted estimates. However, because our results are consistent across cohorts and support a graded association with dose relationship, it is unlikely that residual confounding could explain the findings related to SSBs. For ASBs, however the weaker association and inconsistency between NHS and HPFS, suggest a higher probability of residual confounding. In our study, dietary assessment

was conducted using validated FFQ's. The use of dietary assessment in observational research has been a point of debate due to self-reported intakes and measurement error³⁹. However, assessment of SSB/ASB may be less prone to measurement error since these beverages are relatively easy to measure. Furthermore, our FFQ's have been validated against diet records and biomarkers with reasonable correlations and the use of repeated measures of diet and lifestyle in our analyses could further reduce random measurement error and represent long-term habits. Our study was conducted among a predominately non-Hispanic white population of health professionals, which minimizes potential confounding by socioeconomic factors but may limit generalizability.

In summary, we found that greater intake of SSBs was associated with a higher risk of mortality and showed a graded association with dose. Intake of ASBs was associated with total and CVD mortality at high intake levels mostly among women and warrants further confirmation. Replacing SSB with ASB was associated with a moderately lower risk of mortality. Our results support recommendations and policies to limit intake of SSBs and to consume ASBs in moderation to improve overall health and longevity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors would like to thank the participants and staff of the Nurses' Health Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

Funding Sources: The study was supported by research grants UM1 CA186107, UM1 CA176726, UM1 CA167552, P01 CA87969, P01 CA055075, R01 HL034594, HL088521, HL35464 and HL60712 from the National Institutes of Health.

References

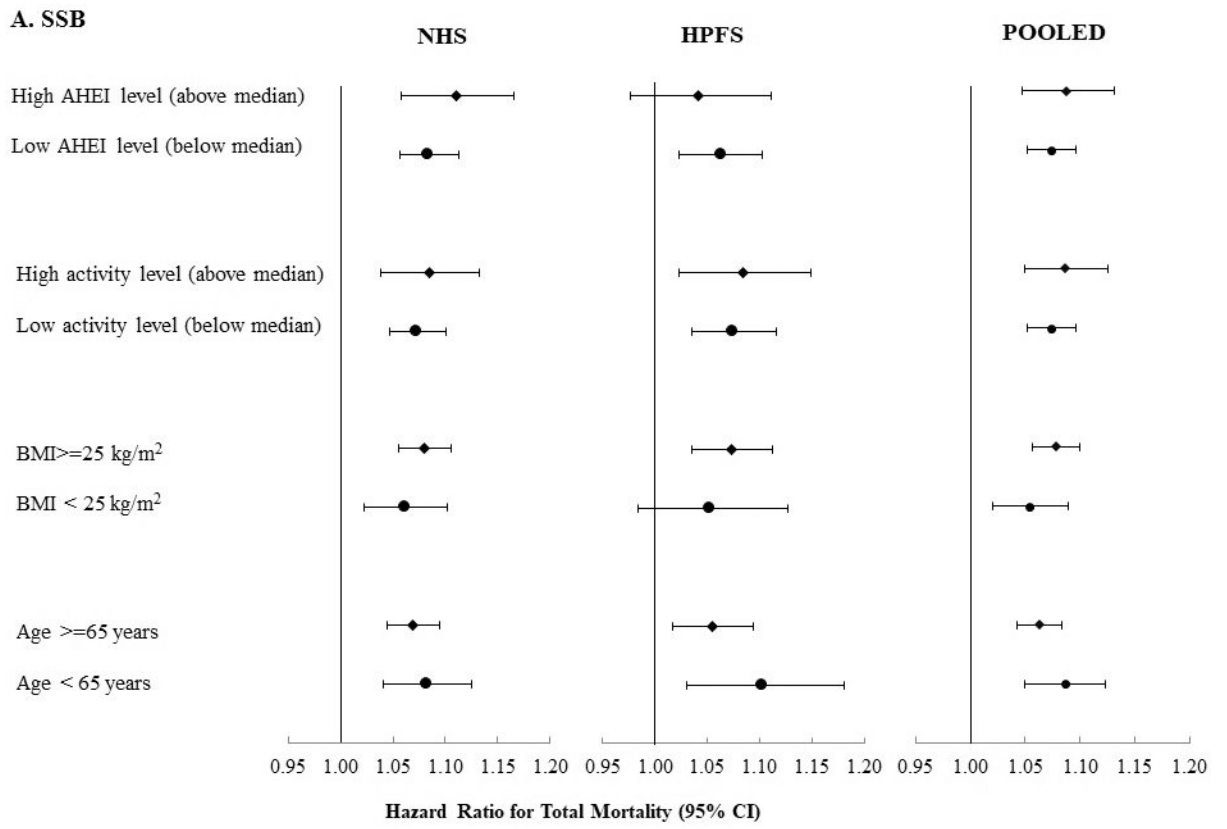
1. Hu FB and Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. *Physiol behav.* 2010;100:47–54. [PubMed: 20138901]
2. NIH. National Cancer Institute: Division of Cancer control & Population Sciences. Epidemiology and Genomics Research Program. Sources of Calories from Added Sugars among the US population, 2005–2006. Updated 4 20, 2018 http://riskfactor.cancer.gov/diet/foodsources/added_sugars/. Accessed 10/02/13.
3. Welsh JA, Sharma AJ, Grellinger L and Vos MB. Consumption of added sugars is decreasing in the United States. *Am J Clin Nutr.* 2011;94:726–734. [PubMed: 21753067]
4. Ogden CL, Kit BK, Carroll MD and Park S. Consumption of sugar drinks in the United States, 2005–2008. *NCHS data brief.* 2011:1–8.
5. Rosinger A, Herrick K, Gahche J and Park S. Sugar-sweetened Beverage Consumption Among U.S. Adults, 2011–2014. *NCHS data brief.* 2017:1–8.
6. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. 12 2015 Available at <http://health.gov/dietaryguidelines/2015/guidelines/>. Accessed 2/4/2019.
7. Malik VS, Willett WC and Hu FB. Global obesity: trends, risk factors and policy implications. *Nat Rev Endocrinol.* 2013;9:13–27. [PubMed: 23165161]

8. Malik VS, Pan A, Willett WC and Hu FB. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr.* 2013;98:1084–1102. [PubMed: 23966427]
9. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC and Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes care.* 2010;33:2477–2483. [PubMed: 20693348]
10. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC and Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr.* 2009;89:1037–1042. [PubMed: 19211821]
11. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC and Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. *Circulation.* 2012;125:1735–1741, S1. [PubMed: 22412070]
12. Bernstein AM, de Koning L, Flint AJ, Rexrode KM and Willett WC. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr.* 2012;95:1190–1199. [PubMed: 22492378]
13. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R and Hu FB. Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults. *JAMA intern med.* 2014;174:516–524. [PubMed: 24493081]
14. Odegaard AO, Koh WP, Yuan JM and Pereira MA. Beverage habits and mortality in Chinese adults. *J Nutr.* 2015;145:595–604. [PubMed: 25733477]
15. Paganini-Hill A, Kawas CH and Corrada MM. Non-alcoholic beverage and caffeine consumption and mortality: the Leisure World Cohort Study. *Prev Med.* 2007;44:305–310. [PubMed: 17275898]
16. de Koning L, Malik VS, Rimm EB, Willett WC and Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *Am J Clin Nutr.* 2011;93:1321–1327. [PubMed: 21430119]
17. Fakhouri TH, Kit BK and Ogden CL. Consumption of diet drinks in the United States, 2009–2010. NCHS data brief. 2012:1–8.
18. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, Sampson L and Willett WC. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr.* 1999;69:243–249. [PubMed: 9989687]
19. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B and Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol.* 1989;18:858–867. [PubMed: 2621022]
20. Yu Z, Ley SH, Sun Q, Hu FB and Malik VS. Cross-sectional association between sugar-sweetened beverage intake and cardiometabolic biomarkers in US women. *Br J Nutr.* 2018;119:570–580. [PubMed: 29508692]
21. Rich-Edwards JW, Corsano KA and Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol.* 1994;140:1016–1019. [PubMed: 7985649]
22. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ and Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr.* 2012;142:1009–1018. [PubMed: 22513989]
23. Bernstein AM, Rosner BA and Willett WC. Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up. *Eur J Epidemiol.* 2011;26:877–86. [PubMed: 22041998]
24. Yu E, Ley SH, Manson JE, Willett W, Satija A, Hu FB and Stokes A. Weight History and All-Cause and Cause-Specific Mortality in Three Prospective Cohort Studies. *Ann Intern Med.* 2017;166:613–620. [PubMed: 28384755]
25. Hu FB. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obes Rev.* 2013;14:606–619. [PubMed: 23763695]
26. Mozaffarian D, Hao T, Rimm EB, Willett WC and Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *New Eng J Med.* 2011;364:2392–2404. [PubMed: 21696306]
27. Winkelmayr WC, Stampfer MJ, Willett WC and Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA.* 2005;294:2330–2335. [PubMed: 16278361]

28. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC and Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004;292:927–934. [PubMed: 15328324]
29. Borrell LN and Samuel L. Body Mass Index Categories and Mortality Risk in US Adults: The Effect of Overweight and Obesity on Advancing Death. *Am J Public Health*. 2014;104:512–519. [PubMed: 24432921]
30. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, Manson JE and Hu FB. Body-mass index and mortality among adults with incident type 2 diabetes. *New Eng J Med*. 2014;370:233–244. [PubMed: 24428469]
31. Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, Freudenheim JL, Giovannucci EL, Goldbohm RA, Jaceldo-Siegl K, Jacobs EJ, Krogh V, Larsson SC, Marshall JR, McCullough ML, Miller AB, Robien K, Rohan TE, Schatzkin A, Sieri S, Spiegelman D, Virtamo J, Wolk A, Willett WC, Zhang SM and Smith-Warner SA. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Nat Cancer Inst*. 2010;102:771–783. [PubMed: 20453203]
32. Schernhammer ES, Hu FB, Giovannucci E, Michaud DS, Colditz GA, Stampfer MJ and Fuchs CS. Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2098–2105. [PubMed: 16172216]
33. de Ruyter JC, Olthof MR, Seidell JC and Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *New Eng J Med*. 2012;367:1397–1406. [PubMed: 22998340]
34. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK and Ludwig DS. A randomized trial of sugar-sweetened beverages and adolescent body weight. *New Eng J Med*. 2012;367:1407–1416. [PubMed: 22998339]
35. Swithers SE. Artificial sweeteners are not the answer to childhood obesity. *Appetite*. 2015;93:85–90. [PubMed: 25828597]
36. Malik VS and Hu FB. Fructose and Cardiometabolic Health: What the Evidence From Sugar-Sweetened Beverages Tells Us. *J Am Coll Cardiol*. 2015;66:1615–1624. [PubMed: 26429086]
37. Rogers PJ, Hogenkamp PS, de Graaf C, Higgs S, Lluch A, Ness AR, Penfold C, Perry R, Putz P, Yeomans MR and Mela DJ. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. *Int J Obes (Lond)*. 2016;40:381–394. [PubMed: 26365102]
38. Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WC and Feskanich D. Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. *Am J Clin Nutr*. 2012;96:1419–1428. [PubMed: 23097267]
39. Satija A, Stampfer MJ, Rimm EB, Willett W and Hu FB. Perspective: Are Large, Simple Trials the Solution for Nutrition Research? *Adv Nutr*. 2018;9:378–387. [PubMed: 30032229]

Clinical Perspective

- 1) What is new:
 - The associations between long-term intake of sugar sweetened beverages (SSBs) and artificially sweetened beverages (ASBs), and risk of total and cause-specific mortality have not been well documented.
 - In two large US cohorts, intake of SSBs was positively associated with total mortality showing a graded association with dose largely due to CVD mortality, and a modest association was observed for cancer mortality.
 - ASB intake was positively associated with total and CVD mortality but not cancer mortality at high intake levels mostly among women and warrants further confirmation.
- 2) What are the clinical implications:
 - Our results provide further support for recommendations and policies to limit intake of SSBs and to consume ASBs in moderation to improve overall health and longevity.
 - ASBs could be used to replace SSBs among habitual SSB consumers but higher consumption of ASBs should be discouraged.
 - Policies and recommendations should continue to call for reductions and limits on SSB intake but should also address alternative beverage options with an emphasis on water.



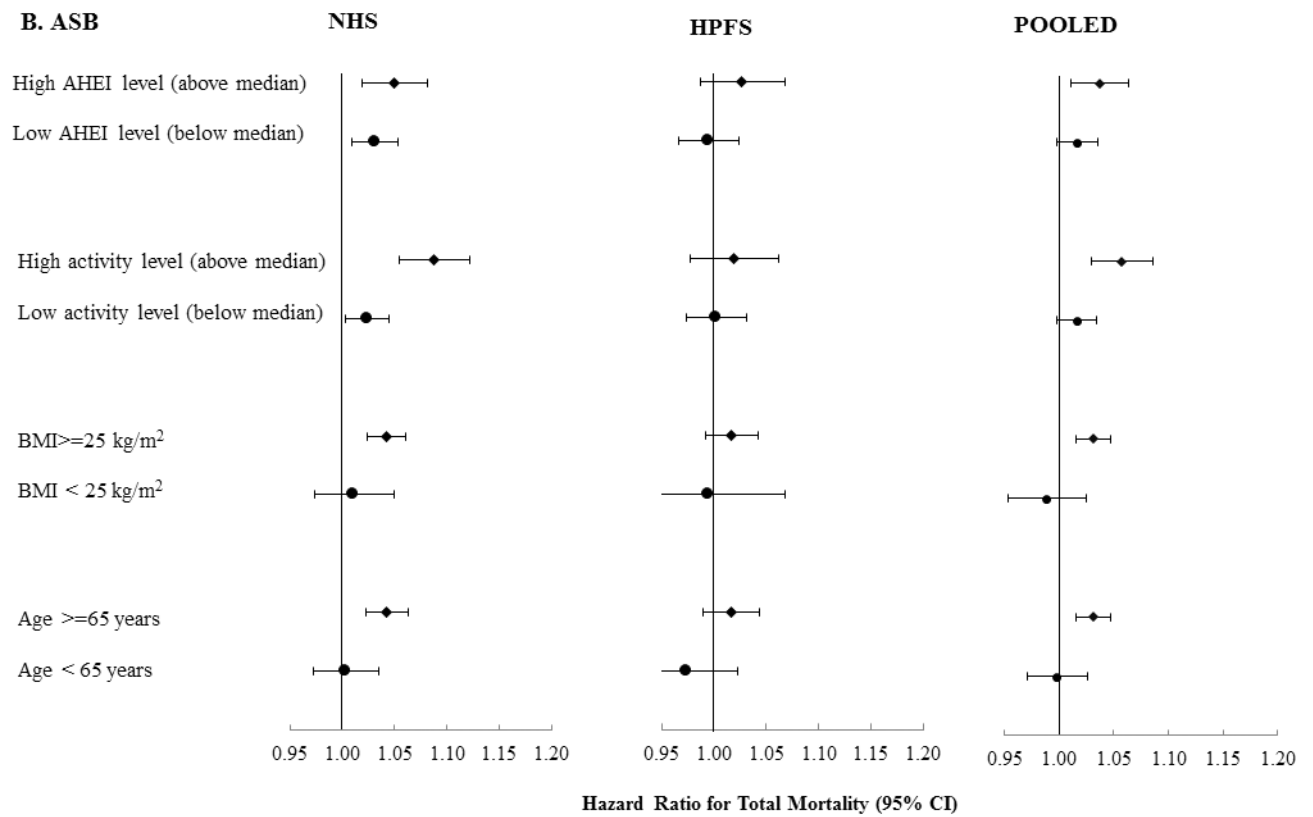


Figure 1: Total Mortality According to SSB Intake (Serving/Day) (A) and ASB (B) Stratified by Age, BMI, Physical Activity and Diet Quality based on pooled data from the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS) and Pooled Data from Both Cohorts.

Adjusted for: age, ASB or SSB, smoking, alcohol intake, postmenopausal hormone use (NHS), physical activity, family history of diabetes, family history of mi, family history of cancer, multivitamin use, ethnicity, aspirin use, baseline history of hypertension and hypercholesterolemia, intakes of whole grains, fruit, vegetables, red and processed meat, total energy and BMI. For SSB, all p-interaction > 0.10 . For ASB, p-interaction > 0.10 except for BMI (p-interaction, 0.01) and physical activity (p-interaction, 0.004) from the pooled analysis and BMI in the NHS (p-interaction, 0.002).

Table 1:

Age-adjusted Characteristics of Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) Participants by Category of Sugar Sweetened Beverage (SSB) and Artificially Sweetened Beverage (ASB) Intake in 1994

	NHS, 1994			HPFS, 1994		
	<1/mo	2-6/wk	2/d	<1/mo	2-6/wk	2/d
SSB Intake (n)	<i>33,641</i>	<i>16,767</i>	<i>2,400</i>	<i>12,832</i>	<i>12,635</i>	<i>1,229</i>
Age*	60.3	59.3	57.6	61.9	59.3	56.1
Body mass index (kg/m ²)	27.4	27.1	28.4	26.9	26.6	26.8
Body mass index (kg/m ²) > 25 %	62	59	65	69	67	66
Physical Activity (Mets/wk)	20.2	18.4	17.6	31.0	29.9	28.1
White race %	98	97	95	96	94	94
Current smoker %	13	14	22	7	7	11
Hypertension % †	14	15	18	20	18	20
High Cholesterol % †	5	4	5	11	9	12
Postmenopausal hormone use %	34	31	25	-	-	-
Aspirin use %	40	41	36	39	38	40
Multivitamin use %	48	46	42	45	43	37
Alcohol (grams/day)	6.1	4.6	4.5	12.3	10.4	9.7
Total energy (kcal/day)	1602	1867	2222	1802	2090	2594
Glycemic load	103	109	132	127	133	157
Whole grains (grams/day)	22.2	17.5	13.1	25.0	19.8	14.5
Fruit (servings/day)	2.3	2.4	2.4	2.4	2.5	2.3
Vegetables (servings/day)	3.5	3.4	3.2	3.3	3.1	2.9
Red and processed meat (servings/day)	0.80	1.1	1.3	0.83	1.14	1.46
Alternative Healthy Eating Index	50.6	47.4	42.7	53.0	49.7	44.2
ASB Intake (n)	<i>30,698</i>	<i>18,434</i>	<i>7,128</i>	<i>16,182</i>	<i>9,607</i>	<i>2,981</i>
Age*	60.7	59.5	57.0	61.3	60.3	56.2
Body mass index (kg/m ²)	26.2	27.8	29.6	25.9	27.1	28.6
Body mass index (kg/m ²) > 25 %	51	66	77	58	74	85
Physical Activity (Mets/wk)	19.1	19.9	17.9	29.4	30.6	30.4
White race %	97	98	98	95	95	96
Current smoker %	18	10	15	9	6	7
Hypertension % †	13	15	19	16	20	25
High Cholesterol % †	4	5	6	9	11	11
Postmenopausal hormone use %	30	36	30	-	-	-
Aspirin use %	38	42	40	36	41	43
Multivitamin use %	45	48	47	42	45	45
Alcohol (grams/day)	5.4	5.2	5.6	11.1	11.4	11.0
Total energy (kcal/day)	1749	1719	1759	2031	1954	2018
Glycemic load	109	106	101	134	131	125

	NHS, 1994			HPFS, 1994		
	<1/mo	2-6/wk	2/d	<1/mo	2-6/wk	2/d
Whole grains (grams/day)	19.3	20.7	17.8	21.4	22.1	19.7
Fruit (servings/day)	2.3	2.4	2.2	2.4	2.4	2.4
Vegetables (servings/day)	3.3	3.6	3.5	3.1	3.2	3.3
Red and processed meat (servings/day)	0.97	0.90	1.02	1.07	0.98	1.07
Alternative Healthy Eating Index	48.4	49.8	46.9	50.0	51.8	49.7

Values are means or percentages and are standardized to the age distribution of the study population.

* not age-adjusted.

[†] Physician-diagnosed condition (yes/no). Mets/wk, metabolic equivalent hours per week.

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Table 2: Total and Cause-specific Mortality According to Intake of Sugar-Sweetened Beverages (SSB) in the Nurses' Health Study (NHS) and Health Professionals Follow-up study (HPFS)

	SSB Category				P trend	HR (95% CI) per 1 serving per day increment
	<1/mo	1-4/mo	2-6/wk	1 to <2/d		
Total Mortality						
Number of cases	11149	5360	4501	1561	861	
Person years	1127585	604268	522058	163412	84884	
Age-adjusted model	1.0	1.02 (0.98, 1.05)	1.10 (1.07, 1.14)	1.34 (1.27, 1.42)	1.63 (1.52, 1.75)	<0.0001
Multivariate model 1	1.0	1.07 (1.04, 1.11)	1.11 (1.07, 1.15)	1.22 (1.16, 1.29)	1.36 (1.27, 1.46)	<0.0001
Multivariate model 2	1.0	1.04 (1.00, 1.07)	1.05 (1.01, 1.09)	1.14 (1.08, 1.20)	1.25 (1.16, 1.34)	<0.0001
HPFS						
Number of cases	5604	2359	3919	809	313	
Person Years	348582	168005	302337	66398	28035	
Age-adjusted model	1.0	0.93 (0.89, 0.98)	1.05 (1.01, 1.10)	1.21 (1.12, 1.30)	1.29 (1.15, 1.44)	<0.0001
Multivariate model 1	1.0	0.97 (0.93, 1.02)	1.09 (1.05, 1.14)	1.20 (1.11, 1.29)	1.21 (1.08, 1.36)	<0.0001
Multivariate model 2	1.0	0.95 (0.91, 1.00)	1.06 (1.01, 1.10)	1.14 (1.05, 1.23)	1.12 (1.00, 1.26)	<0.0001
Pooled						
Age-adjusted model	1.0	0.99 (0.96, 1.01)	1.09 (1.06, 1.12)	1.30 (1.24, 1.35)	1.52 (1.43, 1.61)	<0.0001
Multivariate model 1	1.0	1.03 (1.00, 1.06)	1.10 (1.07, 1.13)	1.20 (1.15, 1.25)	1.30 (1.22, 1.38)	<0.0001
Multivariate model 2	1.0	1.01 (0.98, 1.04)	1.06 (1.03, 1.09)	1.14 (1.09, 1.19)	1.21 (1.13, 1.28)	<0.0001
CVD Mortality						
Number of cases	1883	972	829	293	162	
Age-adjusted model	1.0	1.07 (0.99, 1.16)	1.19 (1.10, 1.29)	1.46 (1.29, 1.65)	1.84 (1.57, 2.17)	<0.0001
Multivariate model 1	1.0	1.12 (1.04, 1.21)	1.19 (1.09, 1.29)	1.31 (1.16, 1.48)	1.51 (1.28, 1.77)	<0.0001
Multivariate model 2	1.0	1.07 (0.99, 1.16)	1.10 (1.01, 1.20)	1.21 (1.06, 1.37)	1.37 (1.16, 1.62)	<0.0001
HPFS						
Number of cases	1593	736	1122	222	84	
Age-adjusted model	1.0	1.02 (0.94, 1.12)	1.09 (1.01, 1.17)	1.22 (1.06, 1.40)	1.33 (1.07, 1.66)	0.0002
						1.11 (1.05, 1.18)

	SSB Category					P trend	HR (95% CI) per 1 serving per day increment
	<1/mo	1-4/mo	2-6/wk	1 to <2/d	2/d		
Multivariate model 1	1.0	1.06 (0.97, 1.16)	1.11 (1.03, 1.20)	1.20 (1.04, 1.38)	1.24 (1.00, 1.55)	0.002	1.08 (1.02, 1.15)
Multivariate model 2	1.0	1.04 (0.95, 1.14)	1.08 (1.00, 1.18)	1.17 (1.01, 1.35)	1.19 (0.95, 1.49)	0.02	1.07 (1.01, 1.14)
Pooled							
Age-adjusted model	1.0	1.05 (0.99, 1.11)	1.14 (1.08, 1.21)	1.35 (1.23, 1.48)	1.63 (1.43, 1.85)	<0.0001	1.18 (1.15, 1.22)
Multivariate model 1	1.0	1.09 (1.03, 1.15)	1.15 (1.08, 1.21)	1.25 (1.14, 1.37)	1.39 (1.22, 1.59)	<0.0001	1.12 (1.08, 1.15)
Multivariate model 2	1.0	1.06 (1.00, 1.12)	1.10 (1.04, 1.17)	1.19 (1.08, 1.31)	1.31 (1.15, 1.50)	<0.0001	1.10 (1.06, 1.14)
Cancer Mortality							
NHS							
Number of cases	3873	2010	1611	532	292		
Age-adjusted model	1.0	1.04 (0.98, 1.10)	1.06 (1.00, 1.12)	1.21 (1.10, 1.32)	1.39 (1.23, 1.56)	<0.0001	1.11 (1.07, 1.15)
Multivariate model 1	1.0	1.10 (1.04, 1.16)	1.08 (1.02, 1.15)	1.14 (1.04, 1.25)	1.22 (1.08, 1.37)	0.0003	1.05 (1.02, 1.09)
Multivariate model 2	1.0	1.06 (1.00, 1.12)	1.03 (0.97, 1.09)	1.08 (0.98, 1.19)	1.16 (1.02, 1.31)	0.02	1.03 (1.00, 1.07)
HPFS							
Number of cases	1678	727	1288	267	102		
Age-adjusted model	1.0	0.94 (0.86, 1.03)	1.10 (1.02, 1.19)	1.23 (1.08, 1.41)	1.26 (1.03, 1.55)	<0.0001	1.12 (1.07, 1.18)
Multivariate model 1	1.0	0.98 (0.89, 1.07)	1.14 (1.06, 1.23)	1.24 (1.09, 1.41)	1.22 (1.00, 1.49)	<0.0001	1.11 (1.05, 1.17)
Multivariate model 2	1.0	0.95 (0.87, 1.04)	1.10 (1.02, 1.19)	1.19 (1.04, 1.36)	1.15 (0.94, 1.42)	0.004	1.08 (1.03, 1.15)
Pooled							
Age-adjusted model	1.0	1.01 (0.97, 1.06)	1.08 (1.03, 1.13)	1.22 (1.13, 1.31)	1.35 (1.22, 1.50)	<0.0001	1.11 (1.08, 1.14)
Multivariate model 1	1.0	1.06 (1.01, 1.11)	1.10 (1.05, 1.15)	1.16 (1.08, 1.25)	1.20 (1.08, 1.33)	<0.0001	1.06 (1.03, 1.09)
Multivariate model 2	1.0	1.03 (0.98, 1.08)	1.06 (1.01, 1.11)	1.12 (1.03, 1.21)	1.16 (1.04, 1.29)	0.0004	1.05 (1.02, 1.08)

Multivariate model 1: adjusted for: age, smoking, alcohol intake, postmenopausal hormone use (NHS), physical activity, family history of diabetes, family history of myocardial infarction, family history of cancer, multivitamin use, ethnicity, aspirin use.

Multivariate model 2: further adjusted for baseline history of hypertension and hypercholesterolemia, intakes of whole grains, fruit, vegetables, red and processed meat, total energy and body mass index. All models adjusted for artificially sweetened beverages.

Table 3: Cause-specific Cancer Mortality According to Intake of Sugar-Sweetened Beverages (SSB) and Artificially Sweetened Beverages (ASB) based on pooled data from the Nurses' Health Study (NHS) and Health Professionals Follow-up study (HPFS)

	Category					P trend	HR (95% CI) per 1 serving per day increment
	<1/mo	1-4/mo	2-6/wk	1 to <2/d	2/d		
SSB							
Total cancer	1.0	1.03 (0.98, 1.08)	1.06 (1.01, 1.11)	1.12 (1.03, 1.21)	1.16 (1.04, 1.29)	0.0004	1.05 (1.02, 1.08)
Lung cancer	1.0	0.96 (0.86, 1.06)	1.04 (0.94, 1.16)	0.86 (0.72, 1.03)	1.07 (0.86, 1.33)	0.73	1.01 (0.94, 1.07)
Colon cancer	1.0	1.01 (0.86, 1.18)	1.07 (0.91, 1.25)	1.05 (0.81, 1.36)	1.38 (0.99, 1.92)	0.07	1.09 (0.99, 1.19)
Breast cancer in women	1.0	1.10 (0.95, 1.26)	1.12 (0.96, 1.30)	1.23 (0.98, 1.53)	1.34 (1.00, 1.80)	0.02	1.09 (1.00, 1.18)
Prostate cancer in men	1.0	1.00 (0.80, 1.25)	1.14 (0.93, 1.39)	0.73 (0.47, 1.14)	0.77 (0.39, 1.52)	0.43	1.01 (0.86, 1.19)
ASB							
Total cancer	1.0	1.01 (0.96, 1.07)	0.99 (0.94, 1.04)	1.00 (0.93, 1.07)	1.04 (0.96, 1.12)	0.58	1.01 (0.98, 1.03)
Lung cancer	1.0	0.96 (0.85, 1.08)	0.85 (0.76, 0.95)	0.93 (0.80, 1.08)	0.92 (0.77, 1.09)	0.20	0.98 (0.92, 1.08)
Colon cancer	1.0	0.97 (0.81, 1.16)	1.01 (0.86, 1.18)	1.11 (0.89, 1.37)	1.01 (0.77, 1.31)	0.69	1.00 (0.91, 1.07)
Breast cancer in women	1.0	1.06 (0.91, 1.23)	0.90 (0.78, 1.05)	0.92 (0.76, 1.13)	1.14 (0.92, 1.40)	0.57	1.01 (0.95, 1.08)
Prostate cancer in men	1.0	0.80 (0.61, 1.06)	1.02 (0.84, 1.25)	0.93 (0.66, 1.32)	1.01 (0.67, 1.52)	0.92	1.02 (0.91, 1.14)

Adjusted for: age, smoking, alcohol intake, postmenopausal hormone use (NHS), physical activity, family history of diabetes, family history of cancer, multivitamin use, ethnicity, aspirin use, baseline history of hypertension and hypercholesterolemia, intakes of whole grains, fruit, vegetables, red and processed meat, total energy and BMI. ASB and SSB were mutually adjusted.

Table 4:

Total and Cause-specific Mortality According to Intake of Artificially Sweetened Beverages (ASB) in the Nurses' Health Study (NHS) and Health Professionals Follow-up study (HPFS)

	ASB Category				P trend	HR (95% CI) per 1 serving per day
	<1/mo	1-4/mo	2-6/wk	1 to <2/d		
Total Mortality						
Number of cases	12561	3550	3981	1858		
Person years	1122996	408370	514864	260369		1482 195608
Age-adjusted model	1.0	0.88 (0.85, 0.91)	0.91 (0.88, 0.94)	1.04 (0.99, 1.09)		1.33 (1.26, 1.41) <0.0001
Multivariate model 1	1.0	0.98 (0.94, 1.02)	0.98 (0.95, 1.02)	1.03 (0.98, 1.09)		1.20 (1.14, 1.27) <0.0001
Multivariate model 2	1.0	0.96 (0.93, 1.00)	0.94 (0.91, 0.98)	0.97 (0.93, 1.02)		1.10 (1.04, 1.16) 0.01
HPFS						
Number of cases	7037	1431	3059	866		611
Person Years	434859	96830	231310	82933		67424
Age-adjusted model	1.0	0.91 (0.86, 0.96)	0.98 (0.94, 1.02)	1.04 (0.97, 1.12)		1.14 (1.05, 1.24) 0.0006
Multivariate model 1	1.0	0.95 (0.90, 1.01)	1.02 (0.98, 1.06)	1.05 (0.97, 1.12)		1.07 (0.99, 1.17) 0.03
Multivariate model 2	1.0	0.95 (0.89, 1.00)	1.00 (0.95, 1.04)	0.98 (0.91, 1.06)		0.99 (0.91, 1.07) 0.85
Pooled						
Age-adjusted model	1.0	0.89 (0.86, 0.91)	0.94 (0.91, 0.96)	1.04 (1.00, 1.08)		1.27 (1.21, 1.33) <0.0001
Multivariate model 1	1.0	0.97 (0.94, 1.00)	1.00 (0.97, 1.03)	1.04 (1.00, 1.08)		1.16 (1.11, 1.21) <0.0001
Multivariate model 2	1.0	0.96 (0.93, 0.99)	0.97 (0.95, 1.00)	0.98 (0.94, 1.03)		1.04 (1.02, 1.12) 0.01
CVD Mortality						
Number of cases	2222	613	691	331		282
Age-adjusted model	1.0	0.87 (0.79, 0.95)	0.92 (0.84, 1.00)	1.10 (0.98, 1.24)		1.59 (1.40, 1.81) <0.0001
Multivariate model 1	1.0	0.96 (0.87, 1.05)	0.99 (0.91, 1.08)	1.09 (0.97, 1.23)		1.41 (1.24, 1.59) <0.0001
Multivariate model 2	1.0	0.90 (0.82, 0.99)	0.89 (0.82, 0.98)	0.95 (0.84, 1.07)		1.15 (1.01, 1.31) 0.08
HPFS						
Number of cases	1975	436	882	280		184
Age-adjusted model	1.0	0.97 (0.88, 1.08)	1.03 (0.95, 1.12)	1.28 (1.13, 1.45)		1.36 (1.17, 1.59) <0.0001
						1.11 (1.07, 1.16)

	ASB Category				P trend	HR (95% CI) per 1 serving per day	
	<1/mo	1-4/mo	2-6/wk	1 to <2/d			
Multivariate model 1	1.0	1.01 (0.91, 1.12)	1.06 (0.98, 1.15)	1.27 (1.12, 1.45)	1.27 (1.09, 1.48)	<0.0001	1.09 (1.05, 1.13)
Multivariate model 2	1.0	0.97 (0.87, 1.08)	0.99 (0.91, 1.07)	1.11 (0.98, 1.26)	1.06 (0.90, 1.23)	0.30	1.03 (0.98, 1.07)
Pooled							
Age-adjusted model	1.0	0.91 (0.85, 0.97)	0.98 (0.92, 1.03)	1.18 (1.08, 1.29)	1.50 (1.36, 1.65)	<0.0001	1.13 (1.10, 1.16)
Multivariate model 1	1.0	0.98 (0.91, 1.05)	1.02 (0.97, 1.09)	1.17 (1.07, 1.27)	1.35 (1.22, 1.48)	<0.0001	1.09 (1.07, 1.12)
Multivariate model 2	1.0	0.93 (0.87, 1.00)	0.95 (0.89, 1.00)	1.02 (0.94, 1.12)	1.13 (1.02, 1.25)	0.02	1.04 (1.01, 1.07)
Cancer Mortality							
NHS							
Number of cases	4154	1334	1520	730	580		
Age-adjusted model	1.0	0.93 (0.87, 0.99)	0.91 (0.86, 0.97)	1.01 (0.93, 1.09)	1.20 (1.10, 1.32)	<0.0001	1.06 (1.03, 1.08)
Multivariate model 1	1.0	1.03 (0.97, 1.09)	0.99 (0.93, 1.05)	1.04 (0.96, 1.12)	1.13 (1.03, 1.23)	0.03	1.03 (1.00, 1.05)
Multivariate model 2	1.0	1.00 (0.94, 1.07)	0.95 (0.90, 1.01)	0.98 (0.91, 1.06)	1.05 (0.96, 1.15)	0.50	1.01 (0.98, 1.04)
HPFS							
Number of cases	2118	469	996	283	196		
Age-adjusted model	1.0	0.99 (0.89, 1.09)	1.01 (0.93, 1.09)	1.01 (0.89, 1.15)	1.05 (0.90, 1.21)	0.54	1.01 (0.97, 1.06)
Multivariate model 1	1.0	1.02 (0.92, 1.13)	1.05 (0.97, 1.13)	1.03 (0.91, 1.17)	1.01 (0.87, 1.17)	0.83	1.01 (0.96, 1.05)
Multivariate model 2	1.0	1.01 (0.92, 1.12)	1.03 (0.95, 1.11)	0.99 (0.87, 1.13)	0.95 (0.82, 1.11)	0.51	0.99 (0.95, 1.03)
Pooled							
Age-adjusted model	1.0	0.94 (0.89, 0.99)	0.95 (0.90, 0.99)	1.01 (0.95, 1.08)	1.16 (1.08, 1.25)	0.0002	1.04 (1.02, 1.07)
Multivariate model 1	1.0	1.03 (0.97, 1.08)	1.01 (0.97, 1.06)	1.04 (0.97, 1.11)	1.10 (1.02, 1.18)	0.04	1.02 (1.00, 1.04)
Multivariate model 2	1.0	1.01 (0.96, 1.07)	0.99 (0.94, 1.04)	1.00 (0.93, 1.07)	1.04 (0.96, 1.12)	0.58	1.01 (0.98, 1.03)

Multivariate model 1: adjusted for: age, smoking, alcohol intake, postmenopausal hormone use (NHS), physical activity, family history of diabetes, family history of myocardial infarction, family history of cancer, multivitamin use, ethnicity, aspirin use.

Multivariate model 2: further adjusted for baseline history of hypertension and hypercholesterolemia, intakes of whole grains, fruit, vegetables, red and processed meat, total energy and body mass index.

All models adjusted for sugar sweetened beverages.