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Associations Between Sugar-Sweetened Beverage Intake and Cardiovascular Disease, Colorectal Cancer, and Mortality: The California Teachers Study

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

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The Dissertation of Lorena Sonia Pacheco is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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ABSTRACT OF THE DISSERTATION

Associations Between Sugar-Sweetened Beverage Intake and Cardiovascular Disease, Colorectal Cancer, and Mortality: The California Teachers Study

by

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Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2019
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Background: Evidence of sugar-sweetened beverage (SSB) consumption and risk of cardiovascular disease (CVD), colorectal cancer (CRC), and mortality is limited and inconsistent, meriting further study.

Methods: This dissertation uses data from the California Teachers Study, a cohort of adult women teachers and administrators (n=133,477; mean ± SD age=54.1 ± 14.8), who were followed from 1995-1996 until incident CVD (myocardial infarction [MI], revascularization, and stroke), CRC, and mortality, through December 31, 2015. SSBs intake was derived from a self-

administered food frequency questionnaire. Annual linkage with state- and nationwide records ascertained end points.

Results: Over 20 years of follow-up, 8,848 incident CVD events (stroke [n=5,258], revascularization [n=2,889], and MI [n=2,677]); 1,318 incident CRC cases; and 14,143 deaths (CVD deaths [n=4,313] and cancer deaths [n=3,457]) were documented. The SSBs and incident CVD results indicated that women who consumed ≥1 serving/day of SSBs had significantly elevated risk of CVD (hazard ratio (HR) [95% confidence interval (CI)]) (1.19 [1.06, 1.34]), revascularization (1.26 [1.04, 1.54]), and stroke (1.21 [1.04, 1.41]) as compared to rare/never consumers. A 42% (1.42 [1.00, 2.01]; *P* trend = 0.021) and 23% (1.23 [1.05, 1.44]; *P* trend = 0.0002) dose-dependent higher risk of CVD was observed in women that consumed ≥1 serving/day of fruit drinks and caloric soft drinks, respectively, versus rare/never consumers. The SSBs and incident CRC findings showed that SSBs were not significantly associated with CRC risk, though a non-significant modest association was suggested. The SSBs and mortality results indicated that compared to rare/never consumers, the multivariable-adjusted HRs [95% CI] were 1.04 [0.94, 1.15] for all-cause, 0.95 [0.75, 1.20] for CVD-specific, and 1.07 [0.90, 1.26] for cancer-specific mortality, in women who consumed ≥1 serving/day of SSBs. There was a dose-dependent increased in all-cause mortality (1.30 [1.14, 1.48]; *P* trend = 0.002) and cancer-specific mortality (1.38 [1.13, 1.69]; *P* trend = 0.029) risk in women who consumed ≥1 serving/day of caloric soft drink compared to rare/never consumers.

Conclusion: Frequent consumption of SSBs, primarily caloric soft drinks, significantly increased the risk of CVD and mortality in adult women, substantiating the evidence on the unfavorable effects of excessive SSB consumption. SSBs are a modifiable dietary component and public health target that can impact preventable CVD and death.

CHAPTER 1:

INTRODUCTION

There is substantial knowledge indicating the function of diet and lifestyle determinants on major chronic diseases.[1–4] Dietary practices influence numerous cardiometabolic health risk factors including those for heart disease, stroke, and type 2 diabetes (T2D), as well as many cancers, considerably affecting and individual's well-being and quality of life and collectively contributing to the health and economic burden of disease.[5–7] Currently, a suboptimal diet is the leading risk factor for morbidity and mortality, and disability, in the United States (U.S.) and worldwide, responsible for more deaths than any other risks globally, including tobacco smoking.[8,9] This diet is characterized by an over-consumption of unfavorable food and beverage items such as sugar-sweetened beverages (SSBs) and processed and red meats, and nutrients including sodium and trans-fat; and an under-consumption of beneficial food groups and nutrients comprising whole grains, fruits, vegetables, nuts and seeds, fiber, legumes, milk, omega-3 fatty acids, and calcium.[9]

SSBs are a major concern since they are a significant source of added sugars in the diet of young and old across the globe.[10] In most Western countries, including high-income European nations, SSBs are the leading source of added sugars.[2] These beverages increase total energy intake while reducing the consumption of other foods including those that are nutrient-rich.[10,11] Moreover, frequent over-consumption of SSBs leads to a caloric surplus, has been associated with an overall unhealthy diet, and ultimately result in weight gain and an increased risk of chronic disease.[2,10,12–14] SSBs are defined as carbonated and noncarbonated manufactured drinks containing any kind of added caloric sweetener or syrup (e.g., high-fructose corn syrup) such as regular soft drinks (not sugar-free or low-calorie or diet), fruit

drinks, sports and energy drinks, sweetened waters, tea and coffee beverages, and electrolyte replacement drinks.[15]

According to the Global Burden of Disease study 2017, a high consumption of SSBs continues to be on the upward trend since 1990, supplying an increased burden of 12.1% (7.02–18.2) between 2007 and 2017 and 17.1% (8.34–28.0) since 1990.[16] A worldwide analysis reported that global SSB consumption in adults over age 20 averaged 0.58 (95% uncertainty interval [UI]: 0.37, 0.89) 8 fluid ounces servings/day.[17] The highest SSB consumption was observed among upper-middle income countries (0.80, 95% UI: 0.51, 1.22 servings/day) followed by lower-middle income countries (0.59, 95% UI: 0.34, 0.95 servings/day). In the same report, males aged 20–39, had the highest intake of daily SSBs (1.04, 95% UI: 0.63, 1.7 servings/day), while females aged 60 and over, had the lowest consumption (0.34, 95% UI: 0.20, 0.53 servings/day). In regards to global regions, SSB consumption was highest in the Americas, predominantly in the Caribbean (1.9, 95% CI: 1.2, 3.0 servings/day) and notably high throughout Central and Andean Latin America, and high-income North America, with average intakes of >0.8 servings/day of SSBs. The lowest SSB intake was observed in East Asia (0.20, 95% CI: 0.16, 0.25 servings/day).[17]

In the U.S., 49.3% of adults consume at least one SSB on a given day, corresponding to 6.5% of total daily calories and as a country, occupying the 26th-highest intake of SSBs worldwide.[17,18] Although the overall nationwide intake of SSBs has considerably declined since early 2000s, these beverages are still responsible for almost half of all added sugars consumed by Americans aged 2 and older.[15] In Latin America, caloric contribution of SSBs primarily affect underserved populations, with at least 10% to as much as 23% of total calorie

consumption.[19,20] Additionally, while intake of SSBs is decreasing in upper-middle income countries, it is still on the rise in Latin America.[21]

The Nutrition and Chronic Diseases Expert Group (NutriCoDE) from the Global Burden of Disease study projected that up to 184,000 (95% UI: 161,000, 208,000) deaths per year could be attributed to habitual over-consumption of SSBs.[22] This analysis also reported that most SSB-related deaths (133,000 [95% UI:126,000, 139,000]) were due to T2D (72.3%), followed by CVD (45,000 [95% UI: 26,000, 61,000] or 24.2%) and body mass index (BMI)-related cancers (6,450 [95% UI: 4,300, 8,600] or 3.5%). Although Latin America and the Caribbean had the highest absolute mortality associated to SSB consumption (48,000 per million adults; 95%UI: 41,000, 54,000), and Australia and New Zealand had the lowest (560; 95%UI: 440, 700), 3 in 4 (75.9%) of all deaths attributable to SSB consumption occurred in low- and middle-income countries. The NutriCoDE group also reported that Mexican men aged 20-44 y had the highest proportional mortality rate, in whom 33.6% (95% UI: 26.4, 39.5%) T2D and BMI-related deaths were associated to SSB consumption. The proportional mortality in adults aged 20-44 y surpassed 20% in Kiribati, Gabon, Marshall Islands, Belize, Barbados, and Tonga. In regards to morbidity, a total of 8.5 (95% UI: 2.8, 19.2) million disability-adjusted life years (DALYs) were related to SSB consumption, with the highest absolute number of SSB-related DALYs observed in lower-middle income countries (4.2; (95% UI: 1.0, 9.1) million DALYs.[22]

Consequently, leading national voluntary health organizations and global health agencies have released sets of recommendations and guidelines on added sugars and SSBs intake.[10,15,23] In the U.S., the U.S. Dietary Guidelines for Americans committee has recommended a reduction in added sugars consumption to <10% of total daily energy intake, exercising caution when selecting sugar-based beverages, and supporting their replacement for

beverages with no added sugars.[15] Similarly, the American Heart Association's (AHA) Scientific Statement on Dietary Sugars and Cardiovascular Health supports a diet that restricts SSB consumption to ≤450 kcal/week and recommends that a total added sugars intake be limited to approximately 5% of total energy (100 kcal/day for women, and 150 kcal/day for men).[23] This is aligned with the organization's *ideal cardiovascular health* concept and bold strategic impact goal by 2020 of reducing cardiovascular disease (CVD)- and stroke-associated deaths by 20% while improving the cardiovascular health of all Americans by 20%.[24] Globally, the World Health Organization (WHO) echoes the U.S. Dietary Guidelines for Americans added sugars recommendations of <10% of total daily energy intake, yet suggests further reductions of <5% of total daily energy intake for additional health benefits.[10] Regardless of these recommendations, Brazil, Canada, South Africa, the UK and the U.S. exceed the WHO's added sugars guidelines. Furthermore, almost 75% of global sugar consumption each year takes place in low- and middle-income countries, which is particularly concerning since these populations have existing health inequities and determinants, disproportionately burdening sub-groups (i.e. children).[10,25]

Together with the effort of these entities to tackle worldwide over-consumption of added sugars and SSBs while promoting healthy diets, health researchers and policymakers have deemed taxation of unhealthy foods and beverages as a potential approach to prevent excessive intake of such items.[19,21,26,27] In regards to SSBs, worldwide implemented actions have stem from a five-domain strategy and includes: taxation of SSBs, particularly regular soft drinks; limiting access to SSBs in schools and public institutions; specific advertising and marketing restrictions targeting children; food labeling rules and public awareness campaigns; and regulations on government purchasing and subsidies, with additional constraints to procurement

of products acquired via government assistant programs.[21,27–30] A recent review of SSBs sales and evaluation of effected policies, found that the most influential actions have been SSB taxation and marketing and advertising restrictions, with taxation on SSBs being the most commonly adopted measure, especially since 2014.[27]

By mid-2015 national level taxes had been achieved in Chile, Mexico, Barbados, Hungary, and France; in four small island states; in the city of Berkeley, California; and in one U.S. Navajo Nation Native-American reservation. Other nations have joined this effort including Australia, Colombia, Ireland, Norway, Philippines, Singapore, South Africa, United Arab Emirates and United Kingdom, as well as several islands and territories.[29,30] SSB taxation fluctuated from 10% in Mexico and France to up to 25% in French Polynesia and other Pacific Islands (Samoa, Mauritius and Tonga), and a two-tier tax in Chile with 18% tax (increased from original 13% in 1980s) for SSBs containing 6.25g added sugar per 100ml and 10% for SSBs with less added sugar.[29–31] Level of applicability was also distinct, taxing to sugar-, caffeine- and salt-containing ready-to-eat foods -and beverages in Hungary or combination of unhealthy foods tax (non-essential) with *soda tax* in Mexico.[27] Evaluation of Mexico's *soda tax* and Berkeley's *penny-per-ounce tax* has provided successful results, demonstrating a 5.5% and 21% decline in purchases of taxed beverages in one year, and a 9.7% and 52.3% reduction by the second year in Mexico and Berkeley, respectively.[32,33] More countries are considering this strategy, and experts project persistent positive long-term outcomes with enactment of taxation of SSBs.

Excessive intake of SSBs as a suboptimal dietary factor, has been associated with adverse health outcomes among ethnically diverse populations and across different ages,[22] becoming a global public health concern.[26,34] A recent systematic review of existing published

evidence led by the WHO reported that consumption of SSBs is a determinant of body weight, and that the observed change in adiposity with increased consumption of SSBs is mediated by total energy intake.[35] Thus, SSBs as a public health concern predominantly stems from their association with weight gain and obesity, and because they solely offer *empty* calories and supply almost no nutritional value.[11,36–41] Consequently, obesity is a significant risk factor for and contributor of morbidity and mortality, most importantly from CVD[42,43] and T2D,[44] but also from chronic kidney disease,[42] numerous cancers,[45] and musculoskeletal disorders[46,47]; thereby comprehensively undertaking SSB consumption as a public health modifiable risk factor for the *public's health.*

The over-consumption of SSBs has been independently associated with CVD and related risk factors including metabolic syndrome and T2D,[13,38,48–52] hypertension,[53–55] coronary heart disease,[56–58] and stroke,[58–62] in large studies with long durations of follow-up. In the Nurses' Health Study, adult women that consumed ≥ 1 SSB per day at baseline, had a 41% greater risk of developing T2D compared to those that consumed of <1 SSB per month (relative risk [RR]= 1.41 [95% CI, 1.09-1.83]; *P* trend <0.001),[38] after 8 years follow-up. In the same cohort, after 24 years follow-up, consuming ≥ 2 SSBs per day, was associated with a 35% greater risk (HR=1.35 [95% CI 1.1, 1.7]) of developing coronary heart disease.[56] In the Framingham Offspring study, after 4 years follow-up, adults that consumed ≥ 1 soft drink per day, had a 22% greater risk of hypertension (hazard ratio [HR]= 1.22 [95% CI 1.05-1.41]), 22% higher risk of hypertriglyceridemia (HR= 1.22 [95% CI 1.07-1.41]) a 22% lower risk of low HDL-cholesterol (HR= 1.22 [95% CI 1.04, 1.44])[51]. Similar CVD-related risk factor HRs has been observed in other U.S. longitudinal cohorts in both men and women. Concerning stroke, published studies have predominantly addressed regular and diet soft drink intake.[59,60] Adult

men and women of the Health Professionals Follow-Up and Nurses' Health Studies that had a regular soft drink intake of ≥1 serving per day compared to none, had a 16% higher risk (HR = 1.16 [95% CI: 1.00, 1.34]) of stroke.[59] Regardless, evidence is still limited on types of SSBs, versus primarily addressing soft drinks, as well as evidence on other CVD hard end points such as revascularization.

SSB consumption has also been examined in relation to several obesity-related and non-obesity-related cancers including renal, bladder, gastric, oral cavity and related organ cancers, pancreatic, colon and colorectal (CRC), and also leukemia and non-Hodgkin's lymphoma.[63–67] Systematic reviews have found a null association between SSBs intake and the risk of these cancers (summary RR = 1.03 [95% CI: 0.96, 1.11]), except for pancreatic cancer (summary RR = 1.12 [95% CI: 0.99; 1.27]) where conflicting findings continue.[63] The impact of SSBs on colon and CRC risk is limited and is slowly building.[68–70] CRC risk has primarily been assessed in relation to dietary patterns and mostly in case-control studies, where SSBs are a contributor of a *Western, Traditional,* or *High-sugar/Unhealthy* derived a posteriori eating pattern.[71–75] Published studies examining SSB consumption and CRC risk prospectively are scarce and needed.[76]

In regards to mortality, there has only been one published study that examined the long-term prospective pooled effect of SSBs and mortality in adult men and women.[77] Data from the Nurses' Health Study and the Healthy Professionals Follow-Up study was analyzed to help fill the gap in the literature on SSB intake, and found a 14% (HR = 1.14 [95% CI: 1.09, 1.19]) and 21% (HR = 1.21 [95% CI: 1.13, 1.28]) higher risk of all-cause mortality, in adults consuming 1-<2/day and ≥2/day servings of SSBs, respectively, versus adults consuming SSBs <1/month, after adjusting for adiposity and other risk factors. The association was observed in CVD-

specific mortality (HR = 1.31 [95% CI: 1.15, 1.50]; *P* trend <0.0001) and cancer-specific mortality (HR = 1.16 [95% CI: 1.04, 1.29]; *P* trend =0.0004).

The three chapters that follow will add to existing literature by examining the association between SSB intake and incidence of leading causes of death, CVD and CRC, and risk of mortality. These studies use data from the California Teachers Study (CTS), an ongoing prospective cohort of 133,477 female teachers and administrators, and members of the California State Teachers Retirement System in 1995-1996. Dietary patterns have been studied in the cohort, however SSB consumption has not been previously analyzed in the CTS. Chapter 2 will focus on incidence CVD, as composite measure including myocardial infarction, revascularization, and stroke, as well as separate sub-end points. Chapter 3 will address CRC risk, differentiating by proximal colon and distal colorectum sites. Chapter 4 will investigate all cause, CVD-specific and cancer-specific mortality, further differentiating by most prevalent CVD disorders and common types of cancer. This dissertation will contribute to the evidence on SSB consumption by: (i) comprehensively addressing CVD events, (ii) building the CRC risk and mortality literature, and (iii) examining specific SSBs.

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CHAPTER 2:

SUGAR-SWEETENED BEVERAGE INTAKE AND CARDIOVASCULAR DISEASE RISK IN THE CALIFORNIA TEACHERS STUDY

ABSTRACT

Background: Evidence of sugar-sweetened beverage (SSB) consumption and cardiovascular disease (CVD) risk is limited and merits further study.

Methods: We examined the prospective association of baseline SSB consumption with incident CVD in 106,178 CVD- and diabetes-free women from the California Teachers Study, a cohort comprised of female teachers and administrators who have been followed since 1995-1996. SSBs were defined as caloric soft drinks, sweetened bottled waters and teas, and fruit drinks (other than fruit juices) and was derived from a self-administered Block95 food frequency questionnaire. SSB consumption was collapsed into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. CVD endpoints (myocardial infarction [MI], stroke, and revascularization) were based on annual linkage with statewide inpatient hospitalization records. Cox proportional hazards models were used to assess the association between SSB consumption and incident CVD, after adjusting for potential confounders and mediators.

Results: Of a total of 8,848 CVD incident cases over 20 years follow-up, the majority were stroke cases (n=5,258), followed by revascularization (n=2,889), and MI (n=2,677). In an age-adjusted model, we observed increased hazard ratios (HR) [95% confidence intervals (CI)] for CVD (1.26 [1.13, 1.42]), MI (1.26 [1.02, 1.55]), revascularization (1.35 [1.12, 1.64]), and stroke (1.26 [1.09, 1.46]) events in women who consumed ≥1 serving/day versus those who rarely/never consumed SSBs. The multivariable-adjusted HR [95% CI] for CVD (1.19 [1.06,

1.34]), revascularization (1.26 [1.04, 1.54]), and stroke (1.21 [1.04, 1.41]) was slightly attenuated, but remained significant in women who consumed ≥1 serving/day of SSBs compared to rare/never consumers. We observed a dose-dependent increased risk of CVD in women who consumed ≥1 serving/day of fruit drinks (1.42 [1.00, 2.01]; *P* trend = 0.021) and caloric soft drinks (1.23 [1.05, 1.44]; *P* trend = 0.0002), compared to rare/never consumers.

Conclusion: Frequent SSB consumption was associated with a higher risk of CVD and related events. SSB intake might be a modifiable dietary target to reduce risk of CVD among women. Future studies should address gender- and racial/ethnically-specific differences as well as changes in SSB consumption over time.

Introduction

Sugar-sweetened beverages (SSBs) are a substantial contributor (almost 50%) of calories as added sugars in the American diet.[1,2] These are manufactured carbonated and noncarbonated beverages containing caloric sweeteners or syrups (e.g., high-fructose corn syrup) and include, but are not limited to, caloric soft drinks (i.e., not sugar-free), fruit drinks, sports and energy drinks, sweetened waters, and tea and coffee beverages with added sugars.[1] The World Health Organization (WHO)[3] and the expert committee of the 2015–2020 Dietary Guidelines for Americans[1] recommend a reduction in added sugars consumption to <10% of total daily energy intake, with the WHO specifically suggesting reductions to <5% of total daily energy intake.[3] The expert committee further highlights discretion when selecting sugar-based beverages, supporting replacement with no-added sugars drinks.[1]

Similarly, the *ideal cardiovascular health* construct conceived by the American Heart Association (AHA) supports a diet that restricts SSB consumption to ≤450 kcal/week and recommends that total added sugars intake be limited to approximately 5% of total energy (100 kcal/day for women [6 teaspoons] and 150 kcal/day for men [9 teaspoons]).[4] The majority of Americans exceed this AHA limit in calories consumed from SSBs. According to the latest report by the National Center for Health Statistics on National Health and Nutrition Examination survey (2011-2014) data, SSBs, on average, contribute 6.5% (~145 kcal) of total caloric intake.[5] Although men are more likely to consume two (16.0%) or three-or-more (8.6%) SSBs compared to women (11.5% or 6.4%, respectively) on a given day, almost 50% of all adults report consuming at least one SSB on any given day.[5]

Consumption of SSBs is positively associated with cardiovascular disease (CVD) risk factors, including weight gain, visceral adiposity and obesity,[6–12] cardiometabolic risk factors

and/or metabolic syndrome and type 2 diabetes,[8,13–18] hypertension,[19–21] and CVD events, such as coronary heart disease (CHD) and stroke,[22–27] among a variety of populations. Although there have been prospective studies addressing the association between SSB intake and CVD end points (e.g., CHD and stroke), they are still limited. In regard to CHD, there have only been four published studies,[22,23,26,27] of which three were adequately powered,[22,23,26] and with an extensive follow-up time. Only one these CHD-focused studies was in an all-female cohort.[22] Concerning stroke, sample size has been impacted when examining gender-specific sub-group analyses in the published literature, affecting precision.[24–27] Moreover, the majority of the stroke-specific literature has assessed a single SSB (i.e., caloric soft drinks). Studies that are able to assess a variety of SSBs and assess incident CVD as an aggregate and as separate sub-end points, should be emphasized.

We aimed to examine the association between SSB consumption and CVD risk, examining incidence of CVD events including myocardial infarction, revascularization, and stroke in a large prospective United States (U.S.) cohort of adult women over a 20-year period. We hypothesized that higher levels of SSB consumption are associated with incident CVD.

Methods

Study Population and Design

The California Teachers Study (CTS) is an ongoing prospective cohort study of 133,477 active and retired female teachers and administrators, who completed a 16-page mailed questionnaire at study enrollment in 1995–1996 and members of the California State Teachers Retirement System.[28] Annual follow-up, mailings, and participant communication capture change of residence. Linkage with the Office of Statewide Health Planning and Development (OSHPD) identifies inpatient hospitalization and – since 2010 – ambulatory, surgery, and

emergency department procedures and diagnoses performed in California. Dates and causes of death are determined via linkage with state and national mortality files and National Death Index.

The CTS has been approved by the Institutional Review Boards at the City of Hope, the University of Southern California, the University of California San Francisco, and the University of California at Irvine. This secondary data analysis was approved by the Institutional Review Boards of City of Hope and the University of California San Diego.

Dietary Assessment and Sugar-Sweetened Beverage Intake

Dietary intake during the year preceding baseline was assessed using a validated 103-item self-administered FFQ, developed from an early version of the Block 95 FFQ that ascertained usual serving size (i.e., small medium, large or extra-large serving) and frequency of consumption (i.e., never or <1 time/month, 1 time/month, 2–3 times/month, 1 time/week, 2 times/week, 3–4 times/week, 5–6 times/week, every day, or ≥2 times/day) of the 103 food and beverage items was characterized. The reproducibility and validity of this instrument in the cohort has been previously published.[29] Estimation of SSB consumption was constituted from 3 items on the FFQ: 'Regular soft drinks (not diet soda)', 'Snapple, Calistoga, sweetened bottled waters or iced teas', and 'Kool-Aid, Hi-C, or other drinks with added Vitamin C'. From the 9 possible frequency categories ranging from 'never' to '≥2 times/day', SSB consumption was collapsed into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. A serving of SSB consisted of 8 fluid ounces (fl oz), approximate weight 237 g, for sweetened bottled water and/or teas and fruit drinks, and 12 fl oz, approximate weight 355 g, for caloric soft drinks.

Ascertainment of Cardiovascular Disease Incidence

CVD incidence was defined as first myocardial infarction (MI, including fatal or non-fatal), revascularization intervention (including coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI] and/or percutaneous transluminal coronary angioplasty [PTCA]) or stroke (fatal or non-fatal) event, after the return of the baseline questionnaire 1995-1996, designated as study start date. Similarly, incidence of each CVD sub-end point: MI, revascularization, and stroke, were defined as first occurrence of each event after completion of baseline questionnaire. Annual linkage with statewide OSHPD hospitalization records, derived medical diagnoses and in-patient procedures for California residents for incident CVD, was completed through December 31, 2015. Participants were followed from study start date until diagnosis with a CVD event as a MI, revascularization procedure (CABG or PCI/PTCA) or stroke, death, moved out of California, or end of follow-up (31 December 2015), whichever came first.

CVD definitions followed the International Statistical Classification of Diseases 9th (ICD-9) and 10th (ICD-10) Revision coding system. The clinical modification (CM) and procedure coding system (PCS) are the adaptation of the ICD-9 and ICD-10 in regards to medical diagnoses and procedures performed in U.S. hospital inpatient health care settings, respectively. Both coding schemes were necessary for a comprehensive ascertainment of CVD outcomes. CM codes denoted physician medical condition, while PCS codes assist in the identification of medical treatment which occurred within a hospital setting. The alphanumeric characters associated with the CM and PCS coding schemes used to define CVD were as follow: MI was defined by ICD-9-CM codes 410.xx, excluding 410.x2 (old MI), and ICD-10-CM codes I21-I22, excluding I25.2 (old MI). CABG was defined by ICD-9-CM code 414.04,

ICD-10-CM code I25-810 and ICD-9-PCS code 36.1x. PCI and/or PTCA were defined by ICD-9-CM code V45.82, ICD-10-CM code Z9861, ICD-9-PCS codes 00.66, 36.06, 36.07, 40.00, with or without 1755, and ICD-10-PCS codes 02703xx, 02713xx, 02723xx, with or without 02C03ZZ and 02C13ZZ. Stroke was defined by ICD-9 codes 430.x, 431.x, 433.x1, 434.x1, 435.x and 436.x, and ICD-10 codes I60.x-I61.x, I63.x-I64.x, G45.x, and I67.

Assessment of Covariates

Self-reported demographic and lifestyle characteristics were collected at baseline as part of enrollment questionnaire and considered as possible confounders. Covariates included age, race/ethnicity, socioeconomic status (SES), smoking status, alcohol intake, family history of CVD (includes myocardial infarction and/or stroke family histories) in first degree relatives (parent, sibling, offspring), moderate-to-vigorous physical activity (MVPA), aspirin frequency and duration, multivitamin frequency and duration, menopausal status and menopausal hormone therapy use, oral contraceptive use, history of hypertension, BMI, total energy intake, and fruit and vegetable intake.

SES was determined by combining three 1990 U.S. block census data variables (occupation, education, and family income); where all block groups in the state were ranked by occupation (% adults employed in managerial/professional occupation), level of education (% of adults over the age of 25 completing at least a college degree), and median family income, corresponding to quartiles analogous the statewide adult population. A summary score was developed for SES with categories ranging from 1 (lowest) to 4 (highest). Smoking status was derived from three questionnaire items addressing cumulative (lifetime) smoking exposure, age when first and last smoked, and average number of cigarettes currently or previously smoked. Alcohol intake was determined from frequency and number of drinks per week of beer,

champagne and/or wine, and cocktails and/or liquor. Physical activity, including MVPA, was estimated using questionnaire-derived intensity, duration, and frequency of listed activities, on an average day. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by height squared (m^2), from self-reported measurements.

Analytic Sample

For this analysis, we excluded participants who specified their data only be used for breast cancer research (n=22), those who resided outside of California at baseline (n=8,851), returned incomplete or incomprehensible questionnaires (n=4), those that had extreme caloric intake values (<600 [n=10,889] or >5000 [n=558] kcal/d) or had incomplete FFQ data at baseline including vitamin use (n=2), were age ≥ 85 years at baseline (n=1,611), those with a history of cardiovascular disease including heart attack, stroke and revascularization procedures (CABG and PCI or PTCA) at or before baseline (n=2,372), and those with a history of diabetes at or before baseline (n=2,994), yielding a final analytic sample of 106,178 female participants for follow-up (Figure 2.1).

Statistical Analyses

Mean and standard error of mean (SEM) or proportion and frequency were calculated for baseline characteristics of cohort participants in each SSB consumption category. Cox proportional hazard modeling was used to estimate HRs (95% CIs) of CVD incidence according to SSB consumption. This approach was also followed for first occurrence of MI, revascularization, and stroke, separate from the first CVD event which included the earliest of the listed CVD sub-end points. The association between type of SSB consumption and incident CVD was also examined. A median method was used to examine the linear trend across intake categories, applied to both semi-quantitative and cups/day analyses. The median intake value of

SSB in each category was designated to all individuals in that category. The statistical significance of the linear trend was tested by Cox proportional hazard model using the median intake value as a continuous independent variable in the multivariable model. The proportional hazards assumption was met by inspecting the survival curves according to SSB consumption categories as well as testing time-varying covariates in the model.

For the multivariable analysis, we adjusted for these potential confounders: age, race/ethnicity (White, Asian/Pacific Islander, African-American, Hispanic, Native-American, or Mixed/Other; further categorized as White vs all other), SES (quartiles: 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, or unknown), smoking status (never, past, current cigarette use [1–12, 13–24, ≥25/day], or unknown use), alcohol intake (0, <20, or ≥20 grams/day), family history of CVD (yes or no), MVPA (quintiles min/week: 0-30, 30-105, 105-210, 210-360, >360, or unknown), aspirin use (did not take regularly, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency, or unknown), multivitamin use (never, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency), menopausal status and menopausal hormone therapy use (premenopausal, perimenopausal/postmenopausal with never, past, or current hormone therapy use of estrogen, estrogen & progesterone, or other hormone combinations), oral contraceptive use (never, past or current), and history of hypertension (yes or no). We further adjusted for possible mediators BMI, total energy intake, and fruit and vegetable intake as a measure of diet quality in separate models. Fruit and vegetable intake was adjusted for total energy by using the residual method,[30] before including it in the model. A total of three progressively adjusted multivariable Cox regression models were fitted after the age-adjusted model. Model 1 included all the above-mentioned covariates except for BMI, total energy intake, and fruit and vegetable intake. Model 2 additionally adjusted for BMI, total energy

intake, and fruit and vegetable intake. The final model is the parsimonious model, keeping a robust set of covariates that were known and tested (if ≥10% change in HR) confounders in this exposure and outcome association. Variables with a p-value ≤0.05 remained in the final model. Additionally, the models examining the association between type of SSB and risk of CVD, were reciprocally adjusted for the other beverage types (i.e., the sweetened water or tea analysis was adjusted for fruit drink and caloric soft drink, and vice versa).

Sensitivity analysis was conducted to further assess dose consumption and enhance intake resolution that could be lost with a semi-quantitative categorization. This included categorization of SSB intake in cups/day (1 cup = 8 fl oz) as: rare/never, up to ½ cup/day, up to 1 cup/day, up to 1 ½ cups/day, and ≥1 ½ cups/day. Additionally, to examine the possibility of reverse causality, CVD events that occurred within the first 2 and 4 years of follow-up were excluded and Cox models were re-ran. This also addressed potential confounding in the association between SSB and CVD (composite), as well as with incident MI, revascularization, and stroke. All *P* values presented are from 2-tailed analyses; $P < 0.05$ was considered statistically significant. Analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

CTS participants were, on average (mean ± SD), aged 52.1 ± 13.4 years, and followed for 1,807,182 person-years to first CVD event. During 20 years of follow-up, we ascertained 8,848 incident cases of CVD; 2,677 incident cases of MI; 2,889 incident cases of revascularization; and 5,258 incident cases of stroke. Among all participants, 4.2% were SSB daily consumers whereas 40.9% of participants reported rarely/never consuming SSBs. Consumption of sweetened bottled water and/or tea, fruit drinks, and caloric soft drinks among

SSB daily consumers was 4.3%, 0.4% and 3.1%, respectively. With respect to demographics and lifestyle factors, participants with the highest SSB intake tended to be younger, married (45.6%), current smokers (7.6%), past or current OC users (72.6%), and averaged (mean ± SEM) 220.1 ± 3.68 minutes/week of MVPA (Table 2.1). With respect to dietary intake and clinical factors, participants with highest SSB intake had a daily higher intake of total energy and carbohydrate, a lower intake of protein, fat, and fruit and vegetables, had the highest obesity rates (17.5%), and more than a fifth had hypertension (14.9%).

After adjusting for CVD risk factors and potential confounders, we observed a positive, statistically significant association between SSB intake and risk of CVD (Table 2.2). Women who were SSB daily consumers had a 18% higher risk of CVD (HR = 1.18 [95% CI: 1.05, 1.32]; *P* trend = 0.019) compared with women who rarely/never consumed SSBs (Model 1, Table 2.2). Further adjusting for BMI, total energy intake, and fruit and vegetable intake (diet quality marker), as potential mediators, attenuated the effect size (HR = 1.16 [95% CI: 1.03, 1.31]; *P* trend = 0.052) (Model 2, Table 2.2), yet the final model showed a 19% higher risk of CVD (HR = 1.19 [95% CI: 1.06, 1.34]; *P* trend = 0.010), among SSB daily consumers compared to those participants that rarely/never consumed SSBs.

The risk of first revascularization event increased by 26% (HR = 1.26 [95% CI: 1.04, 1.54]: *P* trend = 0.037), and the risk of stroke increased by 21% (HR = 1.21 [95% CI: 1.04, 1.41]; *P* trend = 0.056) in daily versus rare/never consumers of SSBs (Final mode, Table 2.2).

With regards to type of SSB, a significant positive association was observed for fruit drinks and caloric soft drinks with incident CVD risk. Women who consumed ≥1 serving/day of fruit drink, had greater CVD (HR = 1.42 [95% CI: 1.00, 2.01; *P* trend = 0.021]) risk, versus those who were rare/never consumers of fruit drinks (Figure 2.2). Similarly, compared to the

rare/never consumers of caloric soft drinks, the intake of ≥1 serving/day of caloric soft drink, increased the risk of CVD by 23% (HR = 1.23 [95% CI: 1.05, 1.44; *P* trend = 0.0002]). We observed a non-significant, positive association for sweetened bottled waters and/or teas consumption and CVD risk. Details on the progressively adjustment models for these beverage-specific associations can be observed in Supplemental Table 2.2.

Sensitivity analysis addressing SSB intake in cups/day showed findings analogous to those of the main analysis. The risk of CVD was similar among those consuming up to 1 ½ cups/day (HR = 1.19 [95% CI: 1.07, 1.34]) and >1 ½ cups/day (HR = 1.22 [95% CI: 1.09, 1.37]; *P* trend = <0.0001) of SSBs compared to rare/never consumers (Final model, Supplemental Table 2.3). The risk of MI increased by 25% (HR = 1.25 [95% CI: 1.02, 1.54]; *P* trend = 0.063), and the risk of stroke by 26% (HR = 1.26 [95% CI: 1.09, 1.46]: *P* trend = 0.001) among women consuming >1 ½ cups/day of SSBs versus rare/never consumers. Revascularization risk was equivalent to main analysis results (Final model, Supplemental Table 2.3).

Sensitivity analyses excluding events which occurred during the first 2 and 4 years of follow-up did not alter the association found between SSB consumption and risk of CVD (Supplemental Table 2.4 and 2.5).

Discussion

We observed a significant positive association between daily consumption of SSBs and risk of CVD event among adult women over a period of 20 years, after adjustment for CVD risk factors, potential confounders, and mediators. We also found a higher risk of revascularization and stroke with daily consumption of SSBs in multivariable models. With regard to specific SSBs, we observed a statistically significant, positive association between caloric soft drink and fruit drink consumption and risk of CVD after covariate adjustment.

The positive dose-dependent association we found between daily SSB intake and risk of CVD is supported by results from a previous longitudinal analysis of SSB consumption and CHD (as nonfatal MI or fatal CHD) in an all-female cohort.[22] Specifically, we found a 19% greater risk (HR = 1.19 [95% CI 1.06, 1.34]) of a CVD event among women who consumed ≥1 SSB serving/day, while Fung et al.,[22] observed a 23% increase risk (RR = 1.23 [95% CI 1.06, 1.43]) in CHD among middle-age women who consumed 1-2 SSB servings/day. We did not observe a statistically significant association between SSB consumption and incident MI following a semi-quantitative exposure categorization, as Fung et al. did,[22] but we did see an association by cups/day classification (HR = 1.25 [95% CI 1.02, 1.54] comparing >1 ½ cups/day versus rare/never) in the sensitivity analysis. This SSB intake is equal to consuming >1 can of caloric 12 fl oz soft drink or >¾ of a 16 fl oz bottle of sweetened water and/or tea or fruit drink, per day. Addressing specific SSBs, we found a positive association between fruit drink (HR = 1.42 [95% CI: 1.00, 2.01]) and soft drink (HR = 1.23 [95% CI: 1.05, 1.44]) intake and incident CVD. Our findings are somewhat corroborated by data from the Nurses' Health Study, where researchers observed a positive association with 2-serving increase in fruit drinks and cola-type carbonated beverages and incident CHD.[22]

In our multivariable-adjusted model, we observed a 26% greater risk (HR = 1.26 [95% CI 1.04, 1.54]) of a revascularization procedure in women who consumed ≥1 serving/day of SSB versus those who rarely/never consume SSBs; with identical risk by cups/day SSB classification. We are unable to compare our revascularization findings with that of others since published literature on this end point is scarce. Alternatively, we might compare our revascularization risk findings with those of MI, since CABG and PCI/PTCA revascularization intervention procedures are representative of a degree of coronary artery disease that leads/has

led to MI. Our HR findings for revascularization and MI risk with SSB intake as cups/day, in fact, were nearly identical. Nonetheless, further research on SSB intake and incident revascularization is warranted.

The association we observed between SSB consumption and stroke (semi-quantitative categorization HR = 1.21 [95% CI: 1.04, 1.41] and sensitivity analysis cups/day HR = 1.26 [95% CI: 1.09, 1.46]) is similar to the finding of Bernstein et al.,[24] who analyzed data from the Nurses' Health Study cohort. In this cohort, women who consumed ≥1 serving/day of sugar-sweetened soda, had a 19% greater risk of total stroke (HR = 1.19 [95% CI 1.05, 1.48]) in comparison to women who reported no SSB intake.[24] While a direct comparison is not possible because of a difference in the exposure variable analyzed (soda vs SSB composite), it is important to note that published data on this end point are scarce. Similarly, using data from a Swedish cohort of adult men and women for followed 10.3 years, Larsson et al.,[25] observed a 19% greater risk of total stroke (RR = 1.19 [95% 1.04, 1.36]) among adults consuming highest (>2 servings/day [200 mL/serving)] versus lowest (0.1 to <0.5 servings/day) SSB intake. In contrast to our findings, the association in their female-only model was statistically insignificant (RR = 1.14 [95% CI: 0.92, 1.41]). Similarly, the female-only model of a Japanese cohort followed for 18 years, comparing almost every day vs rarely/never consumers, reported a HR = 1.21 [95% CI: 0.88, 1.68]).[26]

Our results are partially consistent with recently published meta-analyses assessing the relationship between SSB consumption and CVD risk.[21,31] Xi et al.,[21] pooled data from four prospective cohort studies, including adult men and women, and found a positive association between intake of SSB and risk of CHD where those in the highest SSB consumption group had a 16% greater risk (RR = 1.16 [95% CI: 1.06, 1.27]) of CHD than those in the lowest SSB

consumption group.[21] The CHD definition included other end points including MI. The same meta-analysis found a marginal association between the highest SSB intake and risk of total stroke (RR = 1.10 [95% CI: 1.00, 1.20]), in comparison to lowest SSB intake; with no significant association between SSB consumption and the risk of stroke in dose-response analysis (summary RR = 1.06 [95% CI: 0.97, 1.15] *P* trend > 0.05). Narain et al.,[31] reported that a high SSB intake was associated with a 19% greater risk of MI (RR = 1.19 [95% CI: 1.09, 1.31]) compared to low SSB intake, yet found no effect on risk of stroke (RR = 1.10 [95% CI: 0.97, 1.25]).[31] Interestingly, when stratifying by gender, SSB consumption was only highly associated with ischemic stroke in women (RR = 1.33 [95% CI: 1.07, 1.66]).[31] Our findings are female-specific and can contribute to the literature on SSB intake and stroke incidence, where is suggested that there is a significant difference between genders.

There are several potential biological mechanisms by which SSB intake is linked to CVD risk.[32] A proposed pathway includes the effect of excessive sugar or fructose intake provided by SSBs, greatly augmenting the levels of both glucose and insulin in the bloodstream due to relative postprandial hyperglycemia and increased incretin levels,[33] contributing to, and exacerbating, a high dietary glycemic load (GL). A high GL leads to physiological responses such as appetite stimulation and weigh gain/adiposity, insulin resistance, and glucose intolerance.[34] This state is associated with oxidative stress, disturbed lipid metabolism, and inflammation, leading to endothelial dysfunction and beta cell stress[34–37]; continuing to significantly influence insulin resistance and risk of T2D,[38] as well as the atherosclerotic process and risk of CVD.[35,36,39]

Additionally, fructose is specifically metabolized in the liver, leading to increased hepatic de novo lipogenesis, dyslipidemia, triglyceride production, and visceral adipose tissue

(VAT) accumulation.[40,41] Fructose can also cause elevation of serum uric acid levels, decreasing endothelial nitric oxide and elevating blood pressure, all of which increase CVD risk.[42,43] In our study, we adjusted for both BMI and total energy intake and the association between SSB consumption and incident CVD remained, suggesting that fructose may play a more prominent role in the physiological response of SSB consumption.

It has also been suggested that SSB intake and CVD risk are associated via weight gain. The beverage form of carbohydrates results in an energy surplus, a reduction in satiety due to its liquid form, and the inability to adequately compensate for ingested SSB calories and modify total energy intake.[44,45] A prospective cohort study found that a higher SSB intake (≥1 serving/day) was associated with greater change in VAT volume after 6 years of follow-up, independent of weight gain,[11] which in turn is linked to T2D development and CVD.

Although plausible biological mechanisms on how SSBs might affect CVD risk have been highlighted, we must add that SSB consumption may serve as a surrogate of a suboptimal diet and unfavorable lifestyle. Individuals who frequently consumed SSBs are more likely to follow a Westernized versus prudent dietary pattern, consuming high amount of sodium, saturated fat, meat and sugar, and less amounts of fruit, vegetables, fiber and wholegrain foods, associated with adverse health outcomes.[46–48] In our sample, we observed unfavorable dietary intake and behaviors among women who frequently consumed SSBs, thereby adjustment of these lifestyle factors as well as total energy intake was indispensable.

Our study had several strengths. The prospective collection of data on SSBs, diet, and lifestyle characteristics minimize reverse causation and recall bias, and are strengths of this study. Additionally, sensitivity analysis further addressed possibility of reverse causality. Moreover, data on essential cardiovascular risk factors were collected, allowing us to control for

potential confounders. We also had a large sample size and extended follow-up period. Our ability to annually link with statewide hospitalization and procedure records made for well-defined and characterized end points, minimized participant burden, and reduced bias due to loss to follow-up, are additional study strengths.

In spite of these strengths, a limitation of the study includes being restricted to only a single dietary assessment in which SSB consumption was measured, therefore we recognize the possibility of random measurement error. Additionally, assessment of other beverages, such as artificially sweetened beverages including low-calorie sweet carbonated beverages (diet soft drinks) and other diet carbonated beverages, were not included in the FFQ version used and could not be assessed. Although dietary data were collected prospectively, social desirability bias cannot be disregarded, nor the potential for residual and unmeasured confounding. In addition, we cannot rule out change in beverage consumption intake over time, which we could not measure. SSB consumption trends among U.S. adults has declined in recent years,[49,50] thus considering our findings, we would expect an attenuation in the magnitude of the measure of association with current consumption shifts. In addition, our analyses could have benefited from further adjustment of cardiometabolic risk factors such as blood assay values for total and high-density lipoprotein cholesterol and measured systolic and diastolic blood pressure. Finally, generalizability is limited due to the homogeneous nature of the cohort with respect to gender, race/ethnicity, level of education and occupation.

Conclusion

In conclusion, we found that daily consumption of at least 1 serving of SSBs is associated with a higher risk of CVD, revascularization, and stroke, in women, after accounting for CVD risk factors, sub-optimal lifestyle behaviors and dietary intake. Daily caloric soft drink

consumption increased the risk of first CVD event. In sensitivity analysis, a higher risk of MI was observed among women with a daily intake of >1 ½ cups of SSBs. Our results expand the literature on unfavorable effects of SSB intake, highlighting the importance of intake reduction and change in beverage type consumption patterns.

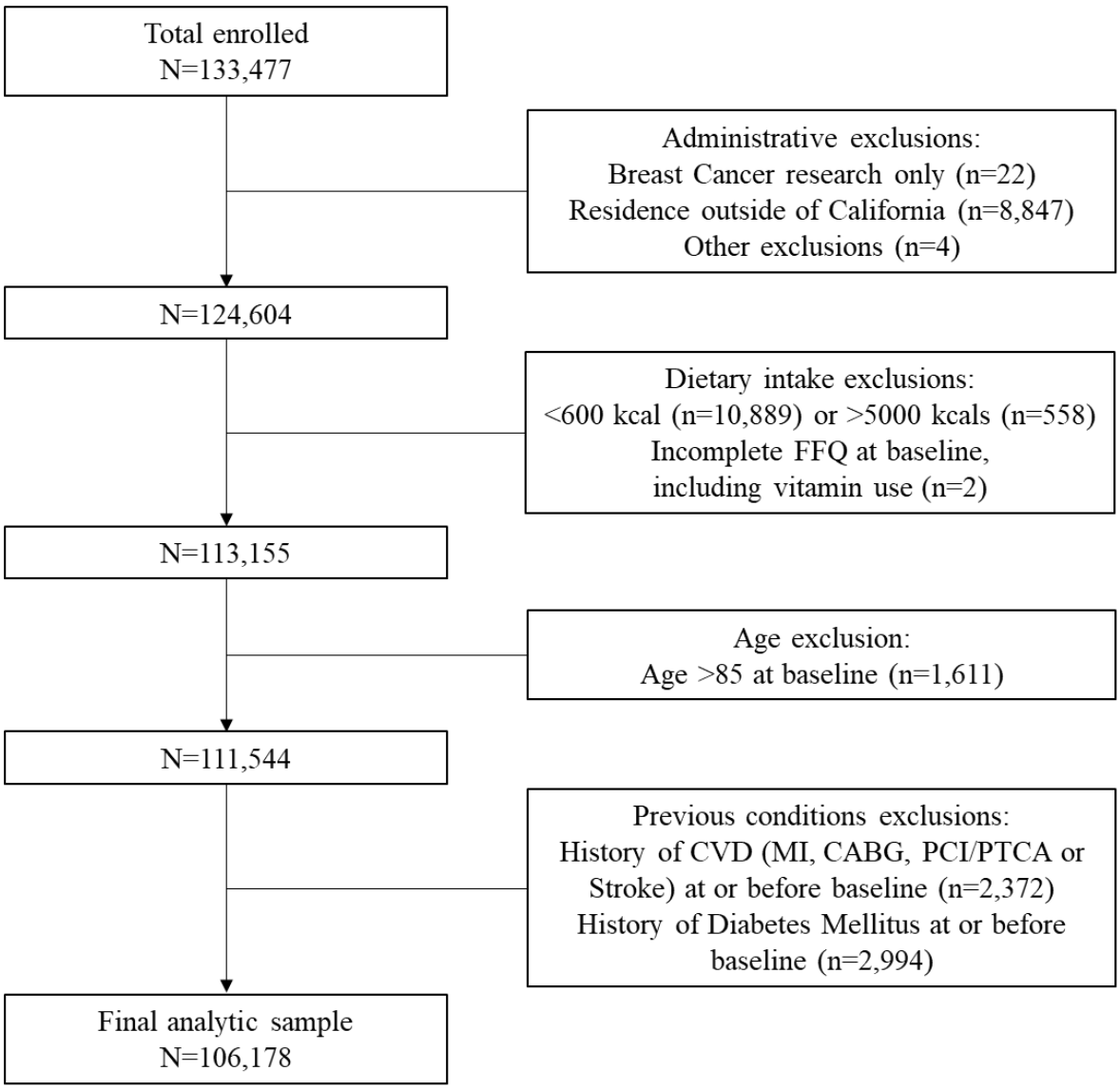

Figure 2.1: Flow-chart showing enrollment, exclusions, and final analytic sample for sugar-sweetened beverage consumption and cardiovascular disease risk in the California Teachers Study.

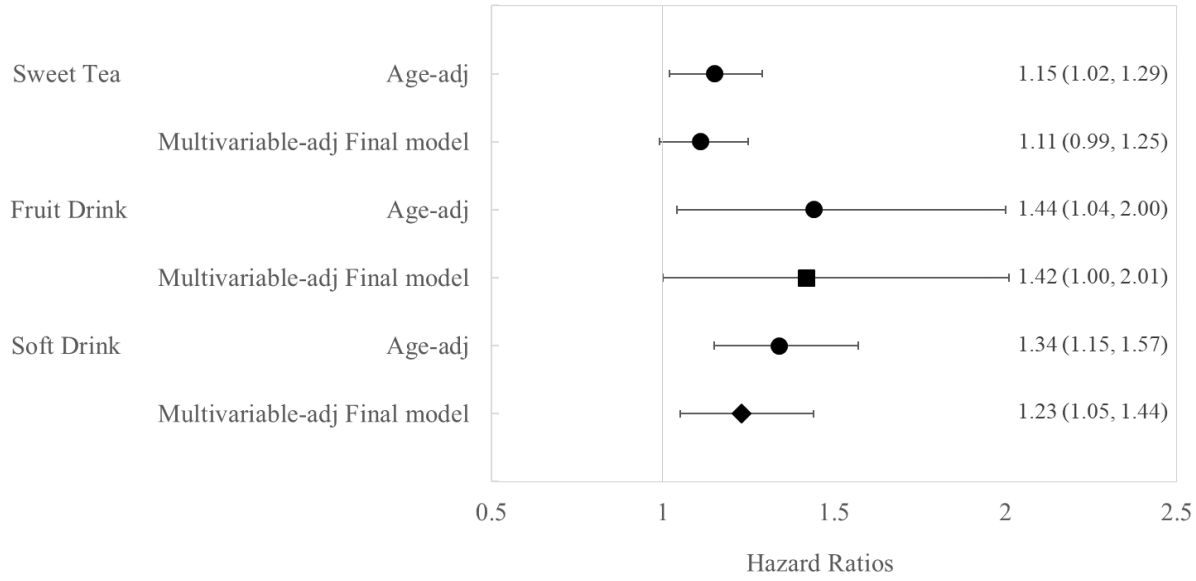

Figure 2.2: Association of specific sugar-sweetened beverage consumption and incident cardiovascular disease. Multivariable-adjusted Final model adjusted for same variables as Final model in Table 2 in addition to consumption of sugar-sweetened bottled water and/or tea, fruit drinks, and caloric soft drinks (other than the main exposure, depending on model). ▪ Indicates *P* trend statistical significance at $P < 0.05$. ♦ Indicates *P* trend statistical significance at $P < 0.001$

Table 2.1: Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories[*] [†]

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	43,425	35,422	22,825	4,506
SSB intake, fl oz/day	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.5 ± 0.05
Dietary Intake				
Energy, kcal/day	1,753.2 ± 3.24	1,949.9 ± 3.59	2,042.6 ± 4.47	2,248.6 ± 10.07
Carbohydrate, g/day	251.4 ± 0.17	253.1 ± 0.19	259.8 ± 0.24	282.3 ± 0.54
Protein, g/day	80.1 ± 0.06	76.7 ± 0.07	74.2 ± 0.09	67.7 ± 0.20
Total Fat, g/day	59.6 ± 0.06	61.4 ± 0.07	59.6 ± 0.09	53.6 ± 0.20
Fruit and vegetable, g/day	361.2 ± 0.84	301.4 ± 0.93	286.7 ± 1.16	265.0 ± 2.61
Age, y	56.0 ± 0.06	49.5 ± 0.07	49.3 ± 0.09	49.0 ± 0.19
Race/ethnicity, %				
White	39,208 (90.3)	29,989 (84.7)	19,500 (85.4)	3,957 (87.8)
All other	4,217 (9.7)	5,433 (15.3)	3,325 (14.6)	549 (12.2)
Education, % ǂ				
Academic/Professional doctorate	1,079 (2.5)	770 (2.2)	522 (2.3)	130 (2.9)
Master's degree	11,130 (25.6)	9,444 (26.7)	6,018 (26.4)	1,210 (26.9)
Bachelor's degree	9,677 (22.3)	8,269 (23.3)	4,804 (21.1)	904 (20.1)
Associate's degree or less	141 (0.3)	147 (0.4)	106 (0.5)	22 (0.5)
Unknown	21,398 (49.3)	16,792 (47.4)	11,375 (49.8)	2,240 (49.7)
Occupation, %				
Teacher, any kind	21,846 (50.3)	22,358 (63.1)	14,708 (64.4)	3,028 (67.2)
Pupil services	1,213 (2.8)	1,155 (3.3)	723 (3.2)	144 (3.2)
Administration	1,401 (3.2)	1,297 (3.7)	926 (4.1)	210 (4.7)
Any other combination	623 (1.4)	648 (1.8)	402 (1.8)	78 (1.7)
Unknown	18,342 (42.2)	9,964 (28.1)	6,066 (26.6)	1,046 (23.2)
Socioeconomic status, %				
1st quartile	1,627 (3.8)	1,565 (4.4)	1,012 (4.4)	189 (4.2)
2nd quartile	7,005 (16.1)	6,147 (17.4)	4,046 (17.7)	755 (16.8)
3rd quartile	13,724 (31.6)	11,737 (33.1)	7,354 (32.2)	1,511 (33.5)
4th quartile	20,524 (47.3)	15,479 (43.7)	10,109 (44.3)	1,997 (44.3)
Unknown	559 (1.3)	504 (1.4)	309 (1.3)	54 (1.2)
Marital status, %				
Married	19,500 (44.9)	17,219 (48.6)	10,581 (46.4)	2,055 (45.6)
Separated or divorced	4,099 (9.4)	3,198 (9.0)	1,958 (8.6)	415 (9.2)
Widowed	3,694 (8.5)	1,742 (4.9)	1,123 (4.9)	199 (4.4)
All other	16,132 (37.2)	13,263 (37.4)	9,163 (40.1)	1,837 (40.8)
MVPA, minutes/week	238.3 ± 1.19	214.4 ± 1.31	221.0 ± 1.63	220.1 ± 3.68
Smoking, current, %	2,222 (5.1)	1,584 (4.5)	1,202 (5.3)	344 (7.6)
Alcohol consumption, ≥20 g/day, %	4,388 (10.1)	2,615 (7.4)	1,767 (7.7)	344 (7.6)
Obese, BMI ≥30 kg/m^2, %	5,462 (12.3)	4,432 (12.4)	3,242 (14.0)	801 (17.5)
Hypertension, %	7,849 (18.1)	4,545 (12.8)	3,130 (13.7)	672 (14.9)
Daily aspirin use, %	3,576 (8.2)	1,821 (5.1)	1,222 (5.4)	285 (6.3)
Daily antihypertensive medication use, %	7,183 (16.5)	3,915 (11.0)	2,730 (12.0)	604 (13.4)
Daily multivitamin use, %	17,723 (40.8)	11,485 (32.4)	7,515 (32.9)	1,584 (35.2)
Cardiovascular disease family history, % §	22,417 (51.6)	15,956 (45.1)	10,346 (45.3)	2,086 (46.3)
Menopausal status and menopausal HT use, %				
Premenopausal	13,143 (30.3)	17,130 (48.4)	10,978 (48.1)	2,151 (47.8)
PP, no HT use	6,349 (14.6)	3,398 (9.6)	2,301 (10.1)	421 (9.3)
PP, past HT use	4,129 (9.5)	2,151 (6.1)	1,359 (6.0)	260 (5.8)
PP, current HT use, Estrogen	6,620 (15.2)	3,864 (10.9)	2,399 (10.5)	492 (10.9)
PP, current HT use, Estrogen & Progesterone	7,203 (16.6)	4,503 (12.7)	2,832 (12.4)	525 (11.7)
PP, all other HT combinations	5,981 (13.8)	4,376 (12.4)	2,956 (13.0)	655 (14.5)
Oral contraceptive use, past and current, %	25,715 (61.5)	24,968 (70.5)	16,235 (71.1)	3,270 (72.6)

*Values are means ± standard error mean or N (percentage). † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Education was obtained after baseline, during fourth mail-in questionnaire follow-up (2005-2006). § Cardiovascular disease family history includes heart attack/myocardial infarction and stroke family history of first-degree relatives (parent, sibling, offspring). Fl oz indicates fluid ounces; g/day, grams per day; HT, hormone therapy; kcal/day, kilocalories per day; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; SSB, sugar-sweetened beverage; y, years.

Table 2.2: Cardiovascular Disease* Risk According to Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories

	Sugar-Sweetened Beverage Consumption †				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Cardiovascular Disease					
No. of cases	4,648	2,382	1,494	324	
Rate per 10,000 person-year	64.8	38.7	37.8	41.4	
Age-adjusted HR (95% CI)	1.0	0.99 (0.95, 1.05)	1.02 (0.96, 1.08)	1.26 (1.13, 1.42)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.00 (0.95, 1.06)	1.01 (0.95, 1.07)	1.18 (1.05, 1.32)	
Model 2	1.0	1.00 (0.95, 1.05)	1.00 (0.94, 1.07)	1.16 (1.03, 1.31)	
Final model	1.0	1.01 (0.96, 1.07)	1.02 (0.96, 1.09)	1.19 (1.06, 1.34)	0.010
Myocardial infarction ǂ					
No. of cases	1,441	681	460	95	
Rate per 10,000 person-year	19.6	10.9	11.5	12.0	
Age-adjusted HR (95% CI)	1.0	0.95 (0.87, 1.04)	1.06 (0.95, 1.18)	1.26 (1.02, 1.55)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.96 (0.87, 1.05)	1.05 (0.94, 1.16)	1.14 (0.92, 1.40)	
Model 2	1.0	0.95 (0.87, 1.06)	1.04 (0.93, 1.16)	1.15 (0.92, 1.43)	
Final model	1.0	0.98 (0.89, 1.07)	1.07 (0.96, 1.19)	1.18 (0.95, 1.47)	0.060
Revascularization §					
No. of cases	1,468	798	505	118	
Rate per 10,000 person-year	20.0	12.8	12.6	14.9	
Age-adjusted HR (95% CI)	1.0	1.01 (0.93, 1.10)	1.03 (0.93, 1.15)	1.35 (1.12, 1.64)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.03 (0.94, 1.12)	1.03 (0.93, 1.15)	1.24 (1.02, 1.50)	
Model 2	1.0	1.04 (0.95, 1.14)	1.02 (0.92, 1.14)	1.23 (1.01, 1.50)	
Final model	1.0	1.05 (0.96, 1.15)	1.04 (0.94, 1.16)	1.26 (1.04, 1.54)	**0.037**
Stroke ǁ					
No. of cases	2,787	1,415	867	189	
Rate per 10,000 person-year	38.2	22.7	21.7	23.9	
Age-adjusted HR (95% CI)	1.0	1.01 (0.94, 1.08)	1.01 (0.93, 1.09)	1.26 (1.09, 1.46)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.02 (0.95, 1.08)	1.00 (0.93, 1.08)	1.19 (1.03, 1.39)	
Model 2	1.0	1.00 (0.94, 1.07)	0.99 (0.92, 1.08)	1.18 (1.01, 1.37)	
Final model	1.0	1.01 (0.95, 1.08)	1.01 (0.93, 1.09)	1.21 (1.04, 1.41)	0.056

*Incident cardiovascular disease event was defined as the first noted myocardial infarction, revascularization (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or stroke, total person-time 1,807,182 years. †1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Total person-time 1,843,233 years. § Revascularization includes coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, total person-time 1,835,429 years.

ǁ Total person-time 1,831,462 years. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and history of hypertension.

Model 2 adjusted for: Model 1 and body mass index, total energy intake, and fruit and vegetable intake.

Final model adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, aspirin use, menopausal status, menopausal hormone therapy use, history of hypertension, body mass index, and total energy intake.

Supplemental Table 2.1: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories[*] [†]

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	43,425	35,422	22,825	4,506
SSB intake, fl oz/day	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.5 ± 0.05
Dietary Intake				
Energy, kcal/day	1,753.2 ± 3.24	1,949.9 ± 3.59	2,042.6 ± 4.47	2,248.6 ± 10.07
Carbohydrate, g/day	251.4 ± 0.17	253.1 ± 0.19	259.8 ± 0.24	282.3 ± 0.54
Protein, g/day	80.1 ± 0.06	76.7 ± 0.07	74.2 ± 0.09	67.7 ± 0.20
Total Fat, g/day	59.6 ± 0.06	61.4 ± 0.07	59.6 ± 0.09	53.6 ± 0.20
Fruit & Vegetables, g/day	361.2 ± 0.84	301.4 ± 0.93	286.7 ± 1.16	265.0 ± 2.61
Age, y	56.0 ± 0.06	49.5 ± 0.07	49.3 ± 0.09	49.0 ± 0.19
Race/ethnicity, %				
Asian/Pacific Islander	1,156 (2.7)	1,593 (4.5)	842 (3.7)	116 (2.6)
African-American	683 (1.6)	1,098 (3.1)	700 (3.1)	121 (2.7)
Hispanic or Latino	1,293 (3.0)	1,758 (5.0)	1,118 (4.9)	195 (4.3)
Native American	337 (0.8)	263 (0.7)	157 (0.7)	29 (0.6)
White	39,208 (90.3)	29,989 (84.7)	19,500 (85.4)	3,957 (87.8)
Other or Mixed	423 (1.0)	473 (1.3)	316 (1.4)	60 (1.3)
Unknown	325 (0.8)	248 (0.7)	192 (0.8)	28 (0.6)
Education, % ǂ				
Academic doctorate	854 (2.0)	598 (1.7)	388 (1.7)	104 (2.3)
Professional doctorate	225 (0.5)	172 (0.5)	134 (0.6)	26 (0.6)
Master's degree	11,130 (25.6)	9,444 (26.7)	6,018 (26.7)	1,210 (26.9)
Bachelor's degree	9,677 (22.3)	8,269 (23.3)	4,804 (21.1)	904 (20.1)
Associate's degree	130 (0.3)	138 (0.4)	98 (0.4)	18 (0.4)
Technical school/certificate/High school	11 (0.0)	8 (0.0)	8 (0.0)	4 (0.1)
Less than High school	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Unknown	21,398 (49.3)	16,792 (47.4)	11,375 (49.8)	2,240 (49.7)
Occupation, %				
Teacher, single grade Pre-K to High school	18,557 (42.7)	19,426 (54.8)	12,770 (56.0)	2,597 (57.6)
Teacher, other	3,009 (6.9)	2,635 (7.4)	1,746 (7.7)	386 (8.6)
Multiple	208 (0.5)	258 (0.7)	152 (0.7)	31 (0.7)
Pupil Services	1,213 (2.8)	1,155 (3.3)	723 (3.2)	144 (3.2)
Administration	1,401 (3.2)	1,297 (3.7)	926 (4.1)	210 (4.7)
Teacher, Pre-K/Elem/Other or JrH/Hi/Other	280 (0.6)	297 (0.8)	192 (0.8)	45 (1.0)
Pupil Services/Administration or Pupil Services/Administration/Teacher combination	415 (1.0)	390 (1.1)	250 (1.1)	47 (1.0)
Unknown	18,342 (42.2)	9,964 (28.1)	6,066 (26.6)	1,046 (23.2)
Socioeconomic status, %				
1st quartile, low	1,627 (3.8)	1,565 (4.4)	1,012 (4.4)	189 (4.2)
2nd quartile, low-medium	7,005 (16.1)	6,147 (17.4)	4,046 (17.7)	755 (16.8)
3rd quartile, medium-high	13,724 (31.6)	11,737 (33.1)	7,354 (32.2)	1,511 (33.5)
4th quartile, high	20,524 (47.3)	15,479 (43.7)	10,109 (44.3)	1,997 (44.3)
Unknown	545 (1.3)	494 (1.4)	304 (1.3)	54 (1.2)
Marital status, %				
Married	19,500 (44.9)	17,219 (48.6)	10,581 (46.4)	2,055 (45.6)
Divorced	3,810 (8.8)	2,902 (8.2)	1,764 (7.7)	380 (8.4)
Separated	289 (0.7)	296 (0.8)	194 (0.9)	35 (0.8)
Widowed	3,694 (8.5)	1,742 (4.9)	1,123 (4.9)	199 (4.4)
Never married	2,069 (4.8)	1,776 (5.0)	1,147 (5.0)	281 (6.2)
Unknown	14,063 (32.3)	11,487 (32.4)	8,016 (35.1)	1,556 (34.5)
MVPA, minutes/week	238.3 ± 1.19	214.4 ± 1.31	221.0 ± 1.63	220.1 ± 3.68
Smoking, %				
Never	27,137 (62.5)	24,695 (69.7)	15,517 (68.0)	2,909 (64.6)
Former	14,012 (32.3)	9,114 (25.7)	6,081 (26.6)	1,248 (27.7)
Current	2,222 (5.1)	1,584 (4.5)	1,202 (5.3)	344 (7.6)
Unknown	54 (0.1)	29 (0.1)	25 (0.1)	5 (0.1)
Number of cigarettes per day, §	13.3 ± 0.08	11.6 ± 0.10	12.0 ± 0.12	14.4 ± 0.26
Alcohol consumption, g/day, %				
None	14,196 (32.7)	11,124 (31.4)	7,353 (32.2)	1,692 (37.6)
<20	24,841 (57.2)	21,683 (61.2)	13,705 (60.0)	2,470 (54.8)
≥20	4,388 (10.1)	2,615 (7.4)	1,767 (7.7)	344 (7.6)

Supplemental Table 2.1: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories[*] [†], Continued

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
Body mass index, kg/m^2, %				
Underweight (<18.5)	1,099 (2.5)	961 (2.7)	580 (2.5)	128 (2.8)
Normal (18.5-24.9)	24,950 (56.4)	21,081 (58.8)	13,093 (56.6)	2,384 (52.1)
Overweight (25-29.9)	10,880 (24.6)	8,311 (23.2)	5,528 (23.9)	1,123 (24.6)
Obese (≥30)	5,462 (12.3)	4,432 (12.4)	3,242 (14.0)	801 (17.5)
Unknown	1,883 (4.3)	1,098 (3.1)	705 (3.1)	139 (3.0)
Hypertension, %	7,849 (18.1)	4,545 (12.8)	3,130 (13.7)	672 (14.9)
Aspirin use, %				
Daily	3,576 (8.2)	1,821 (5.1)	1,222 (5.4)	285 (6.3)
Up to 6 times per week	6,115 (14.1)	5,163 (14.6)	3,381 (14.8)	715 (15.9)
Regular use, unknown frequency	251 (0.6)	181 (0.5)	143 (0.6)	24 (0.5)
Not regularly taken	32,827 (75.6)	27,824 (78.6)	17,790 (78.6)	3,426 (76.0)
Unknown use	656 (1.5)	433 (1.2)	289 (1.3)	56 (1.2)
Antihypertensive medication use, at least 1 medication, %				
Daily	7,183 (16.5)	3,915 (11.0)	2,730 (12.0)	604 (13.4)
Up to 6 times per week	621 (1.4)	445 (1.3)	286 (1.3)	73 (1.6)
Regular use, unknown frequency	524 (1.2)	326 (0.9)	219 (1.0)	43 (1.0)
Not regularly taken	34,441 (79.3)	30,304 (85.6)	19,301 (84.6)	3,730 (82.8)
Unknown use	656 (1.5)	432 (1.2)	289 (1.3)	56 (1.2)
Multivitamin use, %				
Daily	17,723 (40.8)	11,485 (32.4)	7,515 (32.9)	1,584 (35.2)
Up to 6 times per week	6,215 (14.3)	7,126 (20.1)	4,221 (18.5)	692 (15.4)
Never	6,906 (15.9)	5,606 (15.8)	3,635 (15.9)	737 (16.4)
Regular use, unknown frequency	12,581 (29.0)	11,205 (31.6)	7,454 (32.7)	1,493 (33.1)
Myocardial infarction family history, %, ‖	16,909 (38.9)	11,990 (33.9)	7,888 (34.6)	1,597 (35.4)
Stroke family history, %, #	10,775 (24.8)	7,369 (20.8)	4,680 (20.5)	950 (21.1)
Cardiovascular disease family history, %,[**]	22,417 (51.6)	15,956 (45.1)	10,346 (45.3)	2,086 (46.3)
Menopausal status and menopausal HT use, %				
Pre-menopausal	13,143 (30.3)	17,130 (48.4)	10,978 (48.1)	2,151 (47.8)
PP, no HT use	6,349 (14.6)	3,398 (9.6)	2,301 (10.1)	421 (9.3)
PP, past HT use	4,129 (9.5)	2,151 (6.1)	1,359 (6.0)	260 (5.8)
PP, current HT use, Estrogen	6,620 (15.2)	3,864 (10.9)	2,399 (10.5)	492 (10.9)
PP, current HT, Estrogen & Progesterone	7,203 (16.6)	4,503 (12.7)	2,832 (12.4)	525 (11.7)
PP, all other HT combinations	5,981 (13.8)	4,376 (12.4)	2,956 (13.0)	655 (14.5)
Oral contraceptive use, %				
Current	1,543 (3.7)	2,486 (7.0)	1,556 (6.8)	325 (7.2)
Past	24,172 (57.8)	22,482 (63.5)	14,679 (64.3)	2,945 (65.4)
Never	16,043 (38.4)	9,298 (26.3)	5,760 (25.2)	1,063 (24.0)
Unknown if current or past	1,667 (3.8)	1,156 (3.3)	830 (3.6)	173 (3.8)

*Values are means ± standard error mean or N (percentage). † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Education was obtained after baseline, during fourth mail-in questionnaire follow-up (2005-2006). § Current and past smokers only. ‖ Myocardial infarction family history of first-degree relatives (parent, sibling, offspring). # Stroke family history of first-degree relatives (parent, sibling, offspring). ** Cardiovascular disease family history includes heart attack/myocardial infarction and stroke family history of first-degree relatives (parent, sibling, offspring). Elem indicates Elementary; fl oz, fluid ounces; g/day, grams per day; Hi, High School; HT, hormone therapy; JrH, Junior High School; kcal/day, kilocalories per day; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; Pre-K, pre-kindergarten; SSB, sugar-sweetened beverage; y, years.

Supplemental Table 2.2: Cardiovascular Disease* Risk According to Specific Sugar-Sweetened Beverage Consumption

Cardiovascular Disease	Sugar-Sweetened Beverage Consumption †				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Sweetened bottled water and/or tea					
No. of cases	6,224	1,201	1,119	304	
Rate per 10,000 person-years	60.7	33.0	33.3	37.6	
Age-adjusted HR (95% CI)	1.0	0.93 (0.87, 0.99)	0.96 (0.90, 1.03)	1.15 (1.02, 1.29)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.95 (0.89, 1.01)	0.97 (0.90, 1.03)	1.10 (0.98, 1.23)	
Model 2	1.0	0.95 (0.89, 1.01)	0.96 (0.89, 1.02)	1.10 (0.97, 1.24)	
Final model	1.0	0.94 (0.88, 1.01)	0.96 (0.89, 1.02)	1.11 (0.99, 1.25)	0.340
Fruit drinks					
No. of cases	8,268	347	197	36	
Rate per 10,000 person-years	50.9	32.4	29.5	44.6	
Age-adjusted HR (95% CI)	1.0	1.13 (1.01, 1.27)	1.05 (0.91, 1.21)	1.44 (1.04, 2.00)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.12 (1.01, 1.25)	1.04 (0.90, 1.20)	1.38 (0.99, 1.91)	
Model 2	1.0	1.12 (1.00, 1.26)	1.04 (0.89, 1.20)	1.40 (0.99, 1.98)	
Final model	1.0	1.14 (1.02, 1.27)	1.05 (0.91, 1.22)	1.42 (1.00, 2.01)	**0.021**
Caloric soft drinks					
No. of cases	6,428	1,291	960	169	
Rate per 10,000 person-years	54.2	44.1	35.6	29.0	
Age-adjusted HR (95% CI)	1.0	0.98 (0.93, 1.05)	1.09 (1.02, 1.17)	1.34 (1.15, 1.57)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.99 (0.94, 1.06)	1.09 (1.02, 1.17)	1.25 (1.07, 1.45)	
Model 2	1.0	0.99 (0.93, 1.06)	1.09 (1.01, 1.17)	1.17 (1.00, 1.38)	
Final model	1.0	1.01 (0.95, 1.08)	1.12 (1.04, 1.20)	1.23 (1.05, 1.44)	**0.0002**

*Incident cardiovascular disease event was defined as the first noted myocardial infarction, revascularization (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or stroke, total person-time 1,807,182 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. Models were reciprocally adjusted for the other sugar-sweetened beverage types. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and history of hypertension.

Model 2 adjusted for: Model 1 and body mass index, total energy intake, and fruit and vegetable intake.

Final model adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, aspirin use, menopausal status, menopausal hormone therapy use, history of hypertension, body mass index, and total energy intake.

Supplemental Table 2.3: Cardiovascular Disease* Risk According to Sugar-Sweetened Beverage Consumption in Cups per Day

	Rare or never	Up to ½ cup/day	Up to 1 cup/day	Up to 1 ½ cups/day	>1 ½ cups/day	P trend
Cardiovascular Disease						
No. of cases	4,648	2,797	690	356	357	
Rate per 10,000 person-years	64.8	41.0	35.0	37.1	31.3	
Age-adjusted HR (95% CI)	1.0	0.98 (0.93, 1.02)	1.03 (0.95, 1.11)	1.22 (1.09, 1.36)	1.29 (1.16, 1.44)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.98 (0.94, 1.03)	1.02 (0.94, 1.10)	1.18 (1.06, 1.31)	1.21 (1.08, 1.35)	
Model 2	1.0	0.98 (0.94, 1.03)	1.01 (0.92, 1.09)	1.16 (1.04, 1.30)	1.17 (1.05, 1.32)	
Final model	1.0	0.99 (0.95, 1.04)	1.03 (0.94, 1.12)	1.19 (1.07, 1.34)	1.22 (1.09, 1.37)	**<0.0001**
Myocardial infarction†						
No. of cases	1,441	832	206	93	105	
Rate per 10,000 person-years	19.6	12.0	10.3	9.6	9.1	
Age-adjusted HR (95% CI)	1.0	0.97 (0.89, 1.05)	1.04 (0.90, 1.21)	1.09 (0.88, 1.34)	1.33 (1.09, 1.62)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.98 (0.90, 1.06)	1.02 (0.88, 1.18)	1.03 (0.83, 1.27)	1.19 (0.98, 1.46)	
Model 2	1.0	0.98 (0.90, 1.07)	1.00 (0.86, 1.17)	1.00 (0.80, 1.24)	1.18 (0.96, 1.46)	
Final model	1.0	1.00 (0.91, 1.09)	1.04 (0.89, 1.21)	1.04 (0.83, 1.29)	1.25 (1.02, 1.54)	0.063
Revascularization‡						
No. of cases	1,468	934	244	113	130	
Rate per 10,000 person-years	20.0	13.5	12.2	11.7	11.3	
Age-adjusted HR (95% CI)	1.0	0.99 (0.92, 1.08)	1.08 (0.95, 1.24)	1.13 (0.93, 1.37)	1.34 (1.11, 1.60)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	1.01 (0.93, 1.10)	1.08 (0.95, 1.24)	1.10 (0.91, 1.33)	1.25 (1.04, 1.50)	
Model 2	1.0	1.02 (0.94, 1.11)	1.07 (0.93, 1.24)	1.10 (0.90, 1.35)	1.22 (1.01, 1.48)	
Final model	1.0	1.03 (0.95, 1.12)	1.09 (0.95, 1.26)	1.13 (0.92, 1.38)	1.26 (1.04, 1.53)	**0.009**
Stroke§						
No. of cases	2,787	1,669	379	214	209	
Rate per 10,000 person-years	38.2	24.2	19.0	22.1	18.2	
Age-adjusted HR (95% CI)	1.0	0.99 (0.93, 1.05)	0.97 (0.87, 1.08)	1.26 (1.09, 1.45)	1.32 (1.14, 1.52)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	1.00 (0.94, 1.06)	0.96 (0.86, 1.07)	1.23 (1.07, 1.41)	1.25 (1.08, 1.44)	
Model 2	1.0	0.99 (0.93, 1.05)	0.96 (0.85, 1.07)	1.19 (1.03, 1.38)	1.21 (1.04, 1.41)	
Final model	1.0	1.00 (0.93, 1.06)	0.97 (0.87, 1.09)	1.22 (1.06, 1.42)	1.26 (1.09, 1.46)	**0.001**

*Incident cardiovascular disease event was defined as the first noted myocardial infarction, revascularization (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or stroke, total person-time 1,807,182 years. †Total person-time 1,843,233 years. ‡ Revascularization includes coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, total person-time 1,835,429 years. § Total person-time 1,831,462 years. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and history of hypertension.

Model 2 adjusted for: Model 1 and body mass index, total energy intake, and fruit and vegetable intake.

Final model adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, aspirin use, menopausal status, menopausal hormone therapy use, history of hypertension, body mass index, and total energy intake.

Supplemental Table 2.4: Cardiovascular Disease* Risk According to Sugar-Sweetened Beverage Consumption after removal of events that occurred at 2 years follow-up (n=103,518)

	Sugar-Sweetened Beverage Consumption †				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Cardiovascular Disease					
No. of cases	4,353	2,262	1,400	307	
Rate per 10,000 person-years	60.8	36.8	35.5	39.3	
Age-adjusted HR (95% CI)	1.0	1.00 (0.95, 1.05)	1.01 (0.95, 1.08)	1.27 (1.13, 1.42)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.01 (0.96, 1.06)	1.01 (0.96, 1.07)	1.18 (1.05, 1.33)	
Model 2	1.0	1.01 (0.95, 1.06)	1.00 (0.93, 1.06)	1.17 (1.03, 1.32)	
Final model	1.0	1.02 (0.96, 1.07)	1.01 (0.95, 1.08)	1.20 (1.06, 1.35)	**0.019**
Myocardial infarction ǂ					
No. of cases	1,365	652	436	92	
Rate per 10,000 person-years	18.6	10.4	10.9	11.6	
Age-adjusted HR (95% CI)	1.0	0.96 (0.87, 1.05)	1.06 (0.95, 1.18)	1.28 (1.04, 1.59)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.96 (0.88, 1.06)	1.05 (0.94, 1.17)	1.16 (0.94, 1.43)	
Model 2	1.0	0.97 (0.88, 1.07)	1.04 (0.93, 1.17)	1.18 (0.94, 1.47)	
Final model	1.0	0.99 (0.90, 1.09)	1.07 (0.95, 1.20)	1.21 (0.97, 1.51)	**0.048**
Revascularization §					
No. of cases	1,368	757	474	108	
Rate per 10,000 person-years	18.7	12.2	11.9	13.7	
Age-adjusted HR (95% CI)	1.0	1.02 (0.93, 1.11)	1.03 (0.93, 1.14)	1.31 (1.08, 1.60)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.03 (0.94, 1.13)	1.03 (0.92, 1.14)	1.20 (0.99, 1.46)	
Model 2	1.0	1.05 (0.95, 1.15)	1.01 (0.90, 1.13)	1.19 (0.97, 1.46)	
Final model	1.0	1.06 (0.97, 1.16)	1.03 (0.92, 1.15)	1.22 (0.99, 1.50)	0.107
Stroke ‖					
No. of cases	2,634	1,352	817	182	
Rate per 10,000 person-years	36.2	21.7	20.5	23.0	
Age-adjusted HR (95% CI)	1.0	1.01 (0.95, 1.08)	1.00 (0.92, 1.08)	1.27 (1.10, 1.48)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.02 (0.96, 1.09)	1.00 (0.92, 1.08)	1.21 (1.04, 1.41)	
Model 2	1.0	1.01 (0.94, 1.08)	0.99 (0.91, 1.07)	1.19 (1.02, 1.40)	
Final model	1.0	1.02 (0.95, 1.09)	1.00 (0.92, 1.09)	1.22 (1.04, 1.43)	0.069

*Incident cardiovascular disease event was defined as the first noted myocardial infarction, revascularization (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or stroke, total person-time 1,804,121 years. †1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Total person-time 1,840,533 years. § Revascularization includes coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, total person-time 1,832,659 years. ‖ Total person-time 1,828,654 years. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and history of hypertension.

Model 2 adjusted for: Model 1 and body mass index, total energy intake, and fruit and vegetable intake.

Final model adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, aspirin use, menopausal status, menopausal hormone therapy use, history of hypertension, body mass index, and total energy intake.

Supplemental Table 2.5: Cardiovascular Disease* Risk According to Sugar-Sweetened Beverage Consumption after removal of events that occurred at 4 years follow-up (n=100,739)

	Sugar-Sweetened Beverage Consumption †				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Cardiovascular Disease					
No. of cases	3,993	2,094	1,304	286	
Rate per 10,000 person-years	56.1	34.2	33.2	36.8	
Age-adjusted HR (95% CI)	1.0	1.00 (0.94, 1.05)	1.02 (0.95, 1.08)	1.27 (1.12, 1.43)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.01 (0.95, 1.06)	1.01 (0.95, 1.08)	1.18 (1.05, 1.33)	
Model 2	1.0	1.00 (0.95, 1.06)	1.00 (0.94, 1.07)	1.16 (1.02, 1.32)	
Final model	1.0	1.01 (0.96, 1.07)	1.02 (0.96, 1.09)	1.19 (1.05, 1.35)	**0.023**
Myocardial infarction ǂ					
No. of cases	1,272	617	400	86	
Rate per 10,000 person-years	17.4	9.9	10.0	10.9	
Age-adjusted HR (95% CI)	1.0	0.97 (0.88, 1.07)	1.03 (0.92, 1.16)	1.28 (1.03, 1.60)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.97 (0.88, 1.07)	1.02 (0.91, 1.15)	1.16 (0.93, 1.44)	
Model 2	1.0	0.97 (0.88, 1.08)	1.02 (0.91, 1.15)	1.17 (0.93, 1.47)	
Final model	1.0	0.99 (0.90, 1.10)	1.05 (0.93, 1.18)	1.20 (0.96, 1.51)	0.098
Revascularization §					
No. of cases	1,224	699	436	99	
Rate per 10,000 person-years	16.8	11.3	11.0	12.6	
Age-adjusted HR (95% CI)	1.0	1.03 (0.94, 1.13)	1.04 (0.93, 1.16)	1.31 (1.07, 1.62)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.05 (0.95, 1.15)	1.04 (0.93, 1.16)	1.20 (0.98, 1.48)	
Model 2	1.0	1.06 (0.96, 1.17)	1.03 (0.91, 1.15)	1.21 (0.97, 1.49)	
Final model	1.0	1.08 (0.98, 1.19)	1.04 (0.93, 1.17)	1.23 (1.00, 1.53)	0.083
Stroke ‖					
No. of cases	2,447	1,252	775	172	
Rate per 10,000 person-years	33.8	20.2	19.5	21.8	
Age-adjusted HR (95% CI)	1.0	1.00 (0.93, 1.07)	1.01 (0.93, 1.09)	1.28 (1.09, 1.49)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.01 (0.94, 1.08)	1.00 (0.93, 1.09)	1.21 (1.04, 1.42)	
Model 2	1.0	0.99 (0.92, 1.07)	1.00 (0.91, 1.09)	1.18 (1.00, 1.39)	
Final model	1.0	1.00 (0.93, 1.07)	1.01 (0.93, 1.10)	1.21 (1.03, 1.42)	0.066

*Incident cardiovascular disease event was defined as the first noted myocardial infarction, revascularization (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or stroke, total person-time 1,795,512 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Total person-time 1,833,047 years. § Revascularization includes coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, total person-time 1,824,901 years. ‖ Total person-time 1,820,872 years. HR indicates hazard ratio; CI, confidence interval.
Model 1 adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and history of hypertension.
Model 2 adjusted for: Model 1 and body mass index, total energy intake, and fruit and vegetable intake.
Final model adjusted for: age, race/ethnicity, socioeconomic status, smoking status, alcohol intake, cardiovascular disease family history, aspirin use, menopausal status, menopausal hormone therapy use, history of hypertension, body mass index, and total energy intake.

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CHAPTER 3:

SUGAR-SWEETENED BEVERAGES AND COLORECTAL CANCER RISK IN THE CALIFORNIA TEACHERS STUDY

ABSTRACT

Introduction: The association between sugar-sweetened beverage (SSB) consumption and colorectal cancer (CRC) risk remains unclear and published data are limited.

Methods: The analytic cohort included 99,798 women, free of cancer at baseline, from the California Teachers Study, a United States-based longitudinal cohort comprised of 133,477 female teachers and administrators who were active or recently retired members of the California State Teachers Retirement System in 1995. SSB consumption constituted caloric soft drinks, sweetened bottled waters and teas, and fruit drinks, derived from a self-administered food frequency questionnaire. Consumption was divided into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. CRC endpoints were based on annual linkage with California Cancer Registry, defined as first diagnosis of CRC, and classified following the Surveillance, Epidemiology, and End Results Program coding system. Multivariable-adjusted Cox proportional hazards models were used to generate hazard ratios (HR) and 95% confidence intervals (CI) for assessing the association between SSB consumption and incident CRC.

Results: A total of 1,318 incident CRC cases were detected over 20 years of follow-up (54.5% proximal colon and 45.5% distal colorectum). Compared with rare/never consumers, the multivariable-adjusted HR were 1.14 (95% CI = 0.86 to 1.53, *P* trend = 0.26) for total CRC; 1.11 (95% CI = 0.73, 1.68, *P* trend = 0.80) for proximal colon; and 1.22 (95% CI 0.80, 1.86, *P* trend = 0.10) for distal colorectum cancers among women consuming ≥ 1 serving/day of SSBs.

The HR (95% CI) for total CRC was 1.21 (0.91, 1.60) for women consuming ≥1 serving/day of sweetened bottled water and/or tea compared with rare/never consumers.

Conclusion: SSBs were not significantly associated with CRC risk. Future studies should further assess SSBs in large, racial/ethnically diverse cohorts of males and females, and, if feasible, address changes in SSB consumption over time.

Introduction

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in adult men and the second most commonly diagnosed cancer in women.[1] In the United States (U.S.), CRC is the third most frequently occurring malignancy in both adult men and women.[2] Incidence and death rates vary according to nation-specific developmental and economic levels, with an increased burden in transition economies: low-income and middle-income countries, alluding to the influence of environmental and lifestyle factors, such as diet, in the development of CRC.[1,3]

Sugar-sweetened beverage (SSB) consumption has increased worldwide.[4–6] SSBs are manufactured carbonated and noncarbonated beverages containing caloric sweeteners or syrups (i.e. high-fructose corn syrup) and include, but not limited to, caloric soft drinks (not sugar-free), fruit drinks, sports and energy drinks, sweetened waters, and tea and coffee beverages with added sugars.[7] A comprehensive 187-country analysis reported higher per capita SSB consumption in upper-middle vs. lower-middle income countries.[8] Average SSB consumption among U.S. adults was 1.0 serving/day, corresponding to 26th-highest intake of SSBs.[8]

There is substantial evidence that frequent and/or excessive consumption of SSBs leads to weight gain, general obesity and central obesity.[9] This is particularly important since CRC is one of the 13 obesity-related cancers.[10] The Continuous Update Project (CUP), combined effort of the World Cancer Fund and American Cancer Research Institute, concluded that there is strong, convincing evidence of higher body fatness and increased risk of CRC, recommending a healthy weight for risk reduction.[1] Additionally, the CUP recommends limiting the consumption of SSBs while promoting water or unsweetened beverages, with the ultimate goal of excluding SSBs from the diet. In spite of this recommendation, published studies specifically examining

the relationship between SSB intake and risk of colon cancer[11–13] and CRC[14] are limited and inconsistent. A pooled analysis reported a null association between sugar-sweetened carbonated caloric soft drink consumption and colon cancer risk.[15] Results of a prospective study showed sugar-sweetened soft drink consumption was positively associated with risk of CRC.[14]

We examined the association between SSB consumption and incident CRC, including risk by CRC tumor location, in a large prospective cohort of adult women. Our study contributes to the literature by providing data on SSB consumption, as a composite, as well as examining risk for total CRC and by subsite.

Methods

Study Population and Design

The California Teachers Study (CTS) is an ongoing prospective cohort study comprised of 133,477 active and retired female teachers and administrators, who completed a 16-page mailed questionnaire at study enrollment in 1995–1996 and members of the California State Teachers Retirement System. Methodological details of the cohort have been previously published.[16] The baseline questionnaire encompassed a comprehensive range of participant information including demographic and lifestyle characteristics, behavioral factors, family history of chronic disease, medical history and co-morbidities. Annual follow-up questionnaires ascertain change of residence, cancer diagnoses, hospitalizations, ambulatory care procedures, and death. Change of residence is attained by mailings and participant communication. Cancer diagnoses are ascertained by linkage with the California Cancer Registry. Linkage with the Office of Statewide Health Planning and Development provides hospitalization and ambulatory care procedures and diagnoses performed in California. Date of and cause of death are determined using state and national mortality files and National Death Index.

The CTS study was approved by the Institutional Review Boards at the City of Hope, the University of Southern California, the University of California San Francisco, and the University of California at Irvine. This secondary data analysis was approved by the Institutional Review Boards of City of Hope and the University of California San Diego.

Dietary Assessment and Sugar-Sweetened Beverage Intake

Dietary intake during the year preceding baseline was assessed using a validated 103-item self-administered FFQ, developed from a former version of the Block 95 FFQ. Usual serving size (i.e., small medium, large or extra-large serving) and frequency of consumption (i.e., never or <1 time/month, 1 time/month, 2–3 times/month, 1 time/week, 2 times/week, 3–4 times/week, 5–6 times/week, every day, and/or ≥2 times/day) of the 103 food and beverage items was characterized. The reproducibility and validity of this instrument in the cohort has been described elsewhere.[17] SSB consumption determination comprised a composite of sweetened carbonated and noncarbonated beverages, including caloric soft drinks, sweetened bottled waters and/or teas, and fruit drinks (other than fruit juice), derived from 3 items on the FFQ: 'Regular soft drinks (not diet soda)', 'Snapple, Calistoga, sweetened bottled waters or iced teas', and 'Kool-Aid, Hi-C, or other drinks with added Vitamin C'. From the 9 possible frequency categories ranging from 'never or less than once per month' to '≥2 times/day', SSB consumption was collapsed into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. A serving of SSB consisted of 8 fluid ounces (fl oz), approximate weight 237 g, for sweetened bottled water and/or teas and fruit drinks, and 12 fl oz, approximate weight 355 g, for caloric soft drinks.

Ascertainment of Colorectal Cancer Risk

CRC incident cases were identified by linkage with the California Cancer Registry, a statewide population-based cancer registry where cancer diagnoses in California residents are reported that participates in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Annual linkage between a computer-generated list of all CTS cohort participants and the records of Californians with incident cancer in the SEER program registry was completed through December 31, 2015. Incident CRC cases were ascertained by SEER codes, with cancers located in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (SEER codes 21041-21046) categorized as proximal colon and cancers located in the descending colon, sigmoid colon, large intestine, rectosigmoid junction, and rectum (SEER codes 21047-21049, 21051, and 21052) categorized as distal colorectum. Cohort members contributed person-years to the analysis from date of baseline questionnaire completion until first CRC diagnosis date, relocation out of California, death, or December 31, 2015, whichever occurred earliest.

Assessment of Covariates

The baseline questionnaire ascertained demographic and lifestyle characteristics and considered as possible confounders. Covariates included age, race/ethnicity, socioeconomic status (SES), total smoked years, alcohol intake, family history of colorectum cancer in first degree relatives (parent, sibling, offspring), history of polyps, moderate to vigorous physical activity (MVPA), aspirin frequency and duration, multivitamin frequency and duration, menopausal status and menopausal hormone therapy use, oral contraceptive use, BMI, total energy intake, and set of dietary intake covariates.

SES was determined by combining three 1990 U.S. block census data variables (occupation, education, and family income); where all block groups in the state were ranked by occupation (% adults employed in managerial/professional occupation), level of education (% of adults over the age of 25 completing at least a college degree), and median family income, corresponding to quartiles analogous the statewide adult population. A summary score was developed for SES with categories ranging from 1 (lowest) to 4 (highest). Total smoked years was calculated based on age of first and last smoked for those participants who reported smoking at least 100 cigarettes in their lifetime. Alcohol intake was determined from frequency and number of drinks per week of beer, champagne and/or wine, and cocktails and/or liquor. Physical activity, including MVPA, was estimated using questionnaire-derived intensity, duration, and frequency of listed activities, on an average day. BMI (kg/m^2) was calculated as weight (kg) divided by height squared (m^2), from self-reported weight and height measurements.

Analytic Sample

For the current analysis, we excluded participants who specified their data only be used for breast cancer research (n=22), those who resided outside of California at baseline (n=8,847), returned incomplete or incomprehensible questionnaires (n=4), those with a history of cancer at baseline (n=13,660), were age ≥ 85 years at baseline (n=1,681), had extreme caloric intake values (<600 kcal/d [n=8,950] or >5000 kcal/d [n=513]) or had incomplete food frequency questionnaire (FFQ) data at baseline including vitamin use (n=2), yielding a final analytic sample of 99,798 female participants for follow-up (Figure 3.1).

Statistical Analyses

Mean and standard error of mean (SEM) or proportion and frequency were calculated for baseline characteristics of cohort participants in each SSB consumption category. Cox proportional hazard modeling was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of CRC risk according to SSB consumption. The independent associations between type of SSB and incident CRC was also examined; fruit drink consumption is substantially underpower when differentiating by SSB type. Linear trend was modeled by assigning each participant the median intake in her respective SSB intake category and included as a continuous independent variable in the Cox proportional hazard model. The proportional hazards assumption was met by inspecting the survival curves according to SSB consumption categories as well as testing time-varying covariates in the model.

For the multivariate analysis, we adjusted for the following potential confounders: age, race/ethnicity (White, Asian/Pacific Islander, African-American, Hispanic/Latino, Native-American, or Mixed/Other; further categorized as White vs all other), SES (quartiles: 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, or unknown), total smoke years, alcohol intake (0, <20, or ≥20 grams/day), family history of colon cancer (yes or no), history of polyps (yes or no), MVPA (quintiles min/week: 0-30, 30-97.8, 97.8-202.8, 202.8-360, >360, and unknown), aspirin use (1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency, or unknown), multivitamin use (never, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency), menopausal status and menopausal hormone therapy use (premenopausal, perimenopausal/postmenopausal with never, past, or current hormone therapy use of estrogen, estrogen & progesterone, or other hormone combinations), and oral contraceptive use (never, past or current). We further adjusted for the following possible mediators: BMI, total energy

intake, and a set of dietary intake covariates: red meat, processed meat, and non-starchy vegetable. Intake of these three diet components were adjusted for total energy by using the residual method,[18] before including them in the model. A total of three progressively adjusted multivariable Cox regression models were fitted after the age-adjusted model. Model 1 included all the above-mentioned covariates except for BMI, total energy intake, and dietary intake covariates. Model 2 additionally adjusted for BMI, total energy intake and intake of red and processed meat and non-starchy vegetables. The final model is the parsimonious model, keeping a robust set of covariates that were known and tested (if ≥10% change in HR) confounders in this exposure and outcome association. Variables with a p-value ≤0.05 remained in the final model. Additionally, the models examining the association between sweetened bottled waters and/or tea, fruit drink, and caloric soft drink consumption and risk of CRC, were reciprocally adjusted for the other beverage types (i.e. the sweetened water or tea analysis was adjusted for fruit drink and caloric soft drink, and vice versa).

Sensitivity analysis involved further assessment of dose consumption that could be lost with a semi-quantitative categorization. SSB intake was categorized in cups/day (1 cup = 8 fl oz) as: rare/never, up to ½ cup/day, up to 1 cup/day, up to 1 ½ cups/day, and ≥1 ½ cups/day. Additionally, we excluded of CRC cases that occurred within the first 2 and 4 years of follow-up, addressed possible reverse causality and confounding in the association between SSB and incident CRC, and that the observed associations were distorted by pre-existing disease. We also conducted analysis stratified by BMI (underweight, normal weight, overweight, and obese) given biological plausibility supporting stronger effect of SSB in overweight/obese individuals who would have insulin resistance.[19–21] All *P* values presented are 2-tailed; $P < .05$ was

considered statistically significant. Analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

CTS participants were, on average (mean ± SD), aged 52.0 ± 13.5 years, and were followed for a median of 20.1 years, contributing 1,743,453 person-years. During follow-up, we ascertained 1,318 incident cases of CRC, of which 54.5% (n=718) were proximal and 45.5% (n=600) were distal colorectum cases. Table 3.1 reports baseline demographic and lifestyle characteristics for participants according to SSB consumption. Women who consumed ≥1 serving/day of SSBs (SSB daily consumers), which comprised 4.3% of all participants, had an average daily SSB intake of 13.5 ± 0.05 fl oz. These daily consumers tended to have higher intake of total energy, carbohydrate, red and processed meat, and lower intake of protein, fat, and fruit and vegetables compared to the rare/never consumers. They were also more likely to be current smokers (7.6%) with an average (mean ± SEM) total smoke years of 20.3 ± 0.35, past or current OC users (74.8%), premenopausal (47.9%), and had the highest obesity rates (18.2%). Comprehensive participant characteristics are reported in Supplemental Table 3.1.

The HR (95% CI) for total CRC risk and SSB consumption was 1.14 (0.86, 1.53) comparing women who were SSBs daily consumers versus those who rarely/never consumed SSBs (Final model, Table 3.2). The HR (95% CI) for proximal colon cancer was 1.07 (0.71, 1.62) and that for distal colorectum cancer was 1.22 (0.82, 1.83) in the final multivariable-adjusted model (all *P* trend >0.05). There was no statistically significant association between SSB intake and total CRC after taking into account potential confounders including CRC risk factors (Model 1), BMI, and dietary intake (Model 2) (Table 3.2). In regards to type of SSB and CRC, women consuming ≥1 serving/day of sweetened bottled water and/or tea had a HR (95%

CI) for total CRC risk of 1.21 (0.91, 1.60]), compared to those who were rare/never consumers (Table 3.3). Caloric soft drink consumption was not associated with total CRC risk.

Sensitivity analysis addressing SSB intake in cups/day showed a multivariable-adjusted HR (95% CI) for total CRC risk of 1.13 (0.8, 1.49) comparing women who consumed up to 1½ cups/day versus rare/never consumers of SSBs. (Supplemental Table 3.2). Sensitivity analyses excluding events that occurred during the first 2 and 4 years after baseline did not change the direction or significance of the association between SSB consumption and risk of CRC (total, proximal colon cancer, and distal colorectum cancer) (Supplemental Tables 3.3 and 3.4). Also, as noted in the Methods, we assessed SSB intake according to BMI categories to assess the biological hypothesis of a stronger association of SSB and CRC risk in overweight/obese women. We found no evidence in support of this hypothesis (data not shown).

Discussion

Results of this study show no significant association between SSB consumption and total CRC, proximal colon cancer, and distal colorectum cancer. This was consistent regardless of covariate adjustment and remained after removal of CRC cases 2 and 4 years after baseline. Similar results were shown between sweetened bottled water and/or tea consumption and risk of total CRC.

It is challenging to compare our findings with those of the existing literature, since we assessed a composite of SSB consumption, while published studies have mainly addressed caloric soft drink consumption and assessed colon cancer endpoint. Results from the Melbourne Collaborative Cohort Study (MCCS)[14] are consistent with our composite SSB consumption findings on direction of the association, reporting a higher risk of CRC (HR = 1.28 [95% CI 1.04, 1.57]) in individuals consuming ≥1 caloric soft drink/day versus those who never consume

these.[14] Our results are in similar direction and magnitude as those in the MCCS but the HRs lacked precision. In contrast, a meta-analysis[15] pooling primary data on sugar-sweetened carbonated soft drinks from 10 cohorts reported a null association between intake of sugar-sweetened carbonated soft drinks and incident colon cancer (pooled multivariable relative risk [RR] = 0.94 [95% CI 0.66, 1.32]; *P* trend = 0.91), among those consuming >550 g/day (approximately 18 fluid ounces) versus non-consumers.[15] It is important to note that the meta-analysis findings assessed only one type of SSB (i.e. caloric soft drinks) and colon cancer risk. Results of our study show no association between CRC and caloric soft drinks; however, the number of cases in the high intake category was low.

Biological mechanisms for a SSB association with colon or CRC risk have been proposed, including that described by Giovannucci,[22] which might help explain our results and those in the literature. This framework elucidates the inter-relationship and synergy between dietary pattern (versus a single nutrient and/or food), physical activity, and weight status, and how these elements stimulate and/or inhibit hormonal functioning and inflammation and their impact on cancer risk. The insulin/insulin-like growth factor 1 (IGF-1) dyad is considered a key player in the activation and/or regulation of crucial pathways by which mitosis and apoptosis ensue.[23] Hence, hyperinsulinemia and elevated bioavailable IGF-1 levels support a carcinogenic and early tumor growth setting in some cancers, such as in the case of CRC, where this association has been determined, independent of adiposity.[19,24,25] Thus, if insulin is a marker for the causal factor of CRC risk, the entire dietary pattern influencing insulin levels may be expected to be associated with risk of CRC. Indeed, an empirical insulinemic dietary pattern formed in the Nurses' Health Study and Health Professionals Follow-Up Study was associated with about a 30% increased risk of CRC (as well as other digestive system cancers) in these

cohorts.[26] Notably, while SSB did contribute to this dietary pattern, it was only one of 18 items, and the full dietary pattern was high in animal products, refined starches, sugars, and SSBs, while lower in whole grains, whole fruits, and green leafy vegetables.[27] Given that the entire insulinemic dietary pattern yielded a relative risk of about 1.3 for CRC, a single factor such as SSB should yield a relative risk substantially lower than 1.3, assuming insulinemia mediated (or acted as a marker) for the entire effect of SSB on CRC risk. In this context, the modest association we observed is compatible with this hypothesis, albeit the HRs were imprecise.

Our study had several strengths. A large analytic sample allowed us to conduct subgroup analyses by anatomical location; its prospective design addressed recall bias; and due to linkage with SEER cancer registry for endpoint ascertainment, we had a high follow-up rate (>99%). Sensitivity analysis addressed possibility of reverse causality, yet the number of CRC cases was reduced, and affected statistical power. In spite of these strengths, a noteworthy limitation is that our study was likely underpowered due to the small proportion (4.3%) of high SSB consumption (≥1 serving/day). Also, although we presented beverage-specific analysis, the interpretation of such findings is limited due to inadequate sample size; there were few cases of total of CRC, especially in women consuming ≥1 serving/day of fruit drinks and caloric soft drinks. We were also limited to only a single estimate of SSB intake assessed at baseline, thereby we acknowledge the possibility of random measurement error. In addition, we cannot rule out that participants may have changed their beverage consumption intake and changes over time. SSB consumption trends among U.S. adults has declined in recent years,[28,29] thus in comparison to our findings, we would expect an attenuation in the magnitude of the measure of association with current tendencies. Finally, our study population was female and primarily non-Hispanic white, thereby limiting the generalizability of our results to other populations.

Conclusion

In conclusion, we observed a no significant associations between SSB consumption and CRC risk. We propose that future studies repeatedly measure SSBs and address changes in consumption over time. Additionally, we encourage adequately powered cohorts to examine the association between SSBs and CRC risk, and, if possible, address racial/ethnic and gender-specific differences.

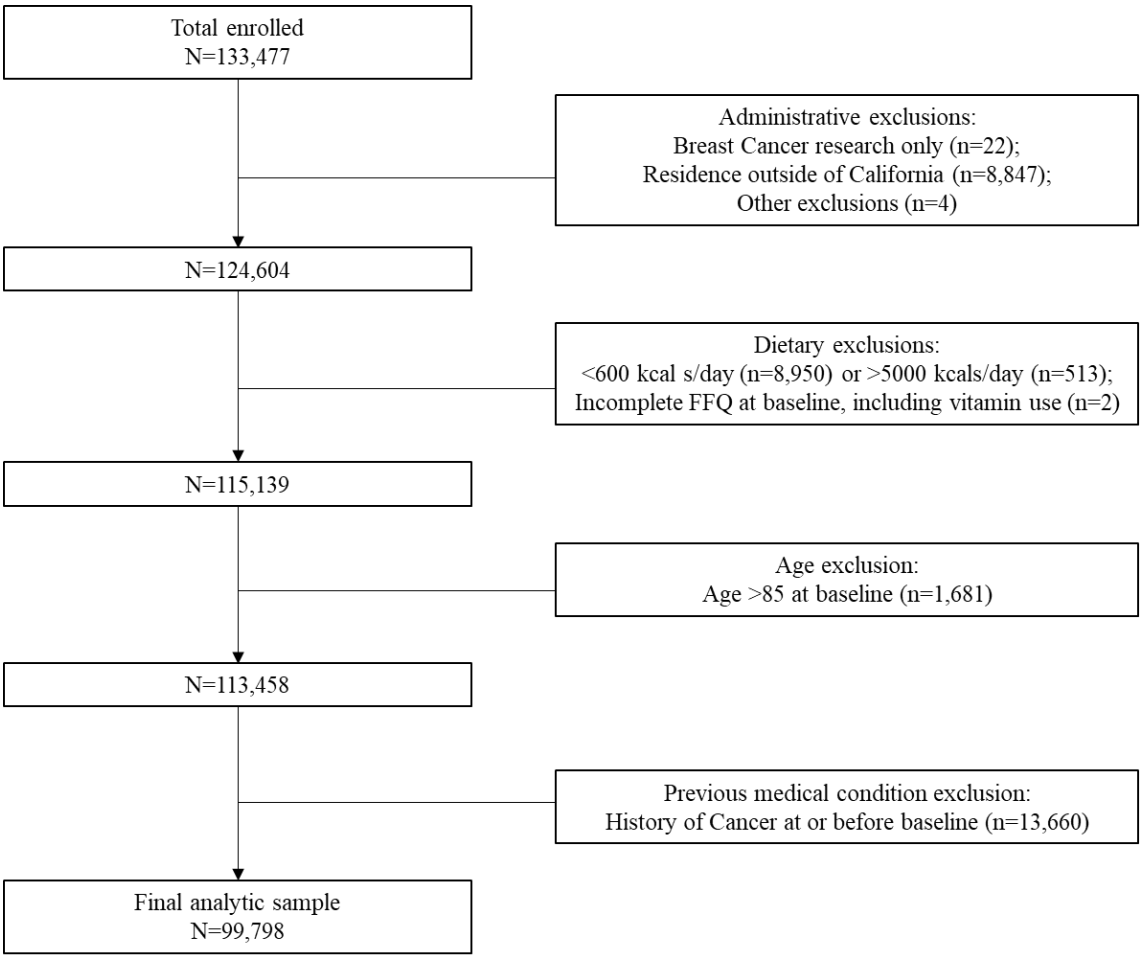

Figure 3.1: Flow-chart showing enrollment, exclusions, and final analytic sample for sugar-sweetened beverages and colorectal cancer risk in the California Teachers Study

Table 3.1: Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	40,911	33,198	21,403	4,286
Age, y	55.5 ± 0.06	48.9 ± 0.07	48.8 ± 0.09	48.8 ± 0.20
Race/ethnicity, %				
White	36,667 (89.6)	27,919 (84.1)	18,147 (84.8)	3,750 (87.5)
All other	4,244 (10.4)	5,279 (15.9)	3,256 (15.2)	536 (12.5)
Education, % ǂ				
Academic/Professional doctorate	1,012 (2.5)	719 (2.2)	494 (2.3)	120 (2.8)
Master's degree	10,494 (25.7)	8,934 (26.9)	5,686 (26.6)	1,150 (26.8)
Bachelor's degree	9,112 (22.3)	7,746 (23.3)	4,518 (21.1)	868 (20.3)
Associate's degree or less	138 (0.3)	139 (0.4)	100 (0.5)	21 (0.5)
Unknown	20,155 (49.3)	15,660 (47.2)	10,605 (49.6)	2,217 (49.6)
Occupation, %				
Teacher, any kind	21,149 (51.7)	21,313 (64.2)	13,968 (65.3)	2,881 (67.2)
Pupil services	1,146 (2.8)	1,099 (3.3)	690 (3.2)	136 (3.2)
Administration	1,311 (3.2)	1,221 (3.7)	866 (4.1)	198 (4.6)
Any other combination	593 (1.5)	602 (1.8)	388 (1.8)	73 (1.7)
Unknown	16,712 (40.9)	8,963 (27.0)	5,491 (25.7)	998 (23.3)
Socioeconomic status, %				
1st quartile, low	1,614 (4.0)	1,493 (4.5)	959 (4.5)	177 (4.1)
2nd quartile, low-medium	6,728 (16.5)	5,846 (17.6)	3,835 (17.9)	718 (16.8)
3rd quartile, medium-high	13,030 (31.9)	11,072 (33.4)	6,891 (32.2)	1,436 (33.5)
4th quartile, high	19,017 (46.5)	14,328 (43.2)	9,435 (44.1)	1,904 (44.4)
Unknown	522 (1.3)	459 (1.4)	283 (1.3)	51 (1.2)
Marital status, %				
Married	18,457 (45.1)	16,268 (49.0)	10,016 (46.8)	1,973 (46.0)
Separated/Divorced	3,831 (9.4)	2,977 (9.0)	1,825 (8.5)	392 (9.2)
Widowed	3,346 (8.2)	1,558 (4.7)	999 (4.7)	178 (4.2)
All other	15,277 (37.3)	12,395 (37.3)	8,563 (40.0)	1,743 (40.7)
Dietary Intake				
Energy, kcal/day	1755.3 ± 3.35	1954.14± 3.72	2046.5 ± 4.64	2255.4 ± 10.36
Carbohydrate, g/day	251.5 ± 0.18	253.4 ± 0.20	260.2 ± 0.25	282.46± 0.55
Protein, g/day	80.6 ± 0.07	76.8 ± 0.07	74.4 ± 0.09	68.0 ± 0.20
Total Fat, g/day	60.0 ± 0.07	61.6 ± 0.07	59.8 ± 0.09	53.8 ± 0.20
Fruit and vegetable, g/day	359.7 ± 0.87	299.9 ± 0.96	285.6 ± 1.19	266.1 ± 2.67
Vegetables, g/day	183.8 ± 0.54	163.4 ± 0.60	163.4 ± 0.74	167.7 ± 1.67
Red meat, g/day	29.4 ± 0.17	34.7 ± 0.19	36.1 ± 0.23	37.3 ± 0.52
Processed meat intake, g/day	6.5 ± 0.06	8.2 ± 0.06	8.5 ± 0.08	8.9 ± 0.18
SSB intake, fl oz	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.5 ± 0.05
MVPA, minutes/week	236.3 ± 1.22	213.7 ± 1.35	219.5 ± 1.68	220.7 ± 3.76
Smoking, current, %	2,084 (5.1)	1,494 (4.5)	1,100 (5.1)	321 (7.5)
Total smoke years ¥	21.1 ± 0.11	17.8 ± 0.14	18.4 ± 0.17	20.0 ± 0.36
Alcohol consumption, ≥20 g/day, %	3,956 (9.7)	2,377 (7.2)	1,602 (7.5)	322 (7.5)
Body mass index, kg/m^2	24.9 ± 0.03	24.6 ± 0.03	25.0 ± 0.04	25.7 ± 0.08
Obese, body mass index ≥30 kg/m^2, %	5,487 (13.4)	4,217 (12.7)	3,079 (14.4)	787 (18.4)
Hypertension, %	7,842 (19.2)	4,288 (12.9)	3,022 (14.1)	673 (15.7)
Diabetes, %	1,712 (4.2)	434 (1.3)	344 (1.6)	109 (2.5)
Daily aspirin use, %	3,656 (8.9)	1,736 (5.2)	1,231 (5.8)	294 (6.9)

Table 3.1: Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*, Continued

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
Daily antihypertensive medication use, %	7,201 (17.6)	3,679 (11.1)	2,622 (12.3)	599 (14.0)
Daily multivitamin use, %	16,355 (40.0)	10,578 (31.9)	6,930 (32.4)	1,492 (34.8)
Cancer family history, % ¤	22,250 (54.4)	17,160 (51.7)	11,083 (51.8)	2,257 (52.7)
Colorectum cancer family history, % §	3,791 (9.3)	2,562 (7.7)	1,711 (8.0)	312 (7.3)
Menopausal status and menopausal HT use, %				
Premenopausal	13,084 (32.0)	16,777 (50.5)	10,722 (50.1)	2,098 (49.0)
PP, no HT	5,639 (13.8)	2,879 (8.7)	1,913 (8.9)	380 (8.9)
PP, past HT	3,241 (7.9)	1,620 (4.9)	1,038 (4.9)	214 (5.0)
PP, current HT Estrogen	6,287 (15.4)	3,567 (10.7)	2,257 (10.6)	480 (11.2)
PP, current HT Estrogen & Progesterone	7,128 (17.4)	4,335 (13.1)	2,739 (12.8)	510 (11.9)
All other	5,532 (13.5)	4,020 (12.1)	2,734 (12.8)	604 (14.1)
Oral contraceptive use, past and current, %	24,524 (62.3)	23,629 (73.4)	15,380 (74.3)	3,097 (75.1)

*Values are n (%) for categorical variables and means ± SEMs for continuous variables. ǂEducation was obtained after baseline, during fourth mail-in questionnaire follow-up, 2005-2006, where a total of n=67,789 participants completed the questionnaire. ¥Former of current smokers. ¤Cancer family history includes breast, endometrial, ovarian, cervical, lung, thyroid, colon, rectal, prostate, melanoma, and skin cancers, and also leukemia, and Hodgkin's lymphoma history, of first-degree relatives (parent, sibling, offspring). §Colorectum cancer family history includes disease in first-degree relatives (parent, sibling, offspring). Elem indicates Elementary; fl oz, fluid ounces; g/day, grams per day; Hi, High School; HT, hormone therapy; JrH, Junior High School; kcal/day, kilocalories per day; mo, months; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; Pre-K, pre-kindergarten; SSB, sugar-sweetened beverage; y, years.

Table 3.2: Colorectal Cancer Risk* According to Sugar-Sweetened Beverage Consumption

	Sugar-Sweetened Beverage Consumption †				
Colorectal Cancer	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Total					
No. of cases	663	354	247	54	
Rate per 10,000 person-years	9.5	6.0	6.5	7.1	
Age-adjusted HR (95% CI)	1.0	0.91 (0.80, 1.04)	1.02 (0.88, 1.18)	1.16 (0.88, 1.53)	
Multivariable-adjusted HR (95% CI)					
Model 1ǂ	1.0	0.92 (0.80, 1.05)	1.01 (0.87, 1.18)	1.15 (0.87, 1.52)	
Model 2¥	1.0	0.91 (0.80, 1.05)	1.04 (0.89, 1.21)	1.16 (0.87, 1.54)	
Final Model¤	1.0	0.92 (0.80, 1.05)	1.04 (0.89, 1.21)	1.14 (0.86, 1.53)	0.259
Proximal Colon					
No. of cases	375	197	120	26	
Rate per 10,000 person-years	5.4	3.7	5.2	3.4	
Age-adjusted HR (95% CI)	1.0	0.97 (0.81, 1.16)	0.94 (0.77, 1.16)	1.08 (0.72, 1.60)	
Multivariable-adjusted HR (95% CI)					
Model 1ǂ	1.0	0.97 (0.81, 1.15)	0.93 (0.76, 1.15)	1.08 (0.72, 1.61)	
Model 2¥	1.0	0.98 (0.81, 1.18)	0.96 (0.78, 1.20)	1.09 (0.72, 1.65)	
Final Model¤	1.0	0.96 (0.80, 1.15)	0.94 (0.76, 1.17)	1.07 (0.71, 1.62)	0.998
Distal Colorectum					
No. of cases	288	157	127	28	
Rate per 10,000 person-years	4.1	2.7	3.4	3.7	
Age-adjusted HR (95% CI)	1.0	0.86 (0.71, 1.05)	1.12 (0.90, 1.38)	1.25 (0.85, 1.85)	
Multivariable-adjusted HR (95% CI)					
Model 1ǂ	1.0	0.85 (0.70, 1.04)	1.09 (0.88, 1.35)	1.22 (0.82, 1.80)	
Model 2¥	1.0	0.85 (0.68, 1.04)	1.11 (0.89, 1.39)	1.22 (0.82, 1.84)	
Final Model¤	1.0	0.87 (0.71, 1.07)	1.14 (0.92, 1.42)	1.22 (0.82, 1.83)	0.101

*Total person-time: 1,743.453 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. HR, hazard ratio; CI, confidence interval.

ǂModel 1 adjusted for: age, race/ethnicity, socioeconomic status, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, diabetes, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use.

¥Model 2 adjusted for: Model 1 and body mass index, total energy intake, and dietary variables: red meat, processed meat, and vegetable intakes.

¤Final model: age, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, multivitamin use, menopausal status, menopausal hormone therapy use, body mass index, and total energy intake.

Table 3.3: Colorectal Cancer Risk* According to Specific Sugar-Sweetened Beverage Consumption

Total Colorectal Cancer	Sugar-Sweetened Beverage Consumption †				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Sweetened bottled water and/or tea					
No. of cases	876	201	185	56	
Rate per 10,000 person-years	8.8	5.7	5.7	7.2	
Age-adjusted HR (95% CI)	1.0	0.82 (0.82, 1.13)	0.97 (0.83, 1.15)	1.23 (0.94, 1.61)	
Multivariable-adjusted HR (95% CI)					
Model 1‡	1.0	0.98 (0.84, 1.15)	0.99 (0.84, 1.17)	1.24 (0.94, 1.62)	
Model 2¥	1.0	0.98 (0.83, 1.15)	0.99 (0.84, 1.17)	1.24 (0.93, 1.64)	
Final model¤	1.0	0.97 (0.82, 1.14)	0.98 (0.83, 1.16)	1.21 (0.91, 1.60)	0.287
Fruit drinks					
No. of cases	1,233	53	30	2	
Rate per 10,000 person-years	7.9	5.1	4.6	2.5	
Age-adjusted HR (95% CI)	1.0	0.97 (0.73, 1.28)	0.89 (0.62, 1.28)	0.45 (0.11, 1.81)	
Multivariable-adjusted HR (95% CI)					
Model 1‡	1.0	0.95 (0.72, 1.26)	0.87 (0.60, 1.25)	0.44 (0.11, 1.77)	
Model 2¥	1.0	0.91 (0.68, 1.21)	0.91 (0.63, 1.32)	0.48 (0.12, 1.91)	
Final model¤	1.0	0.93 (0.69, 1.24)	0.93 (0.64, 1.34)	0.48 (0.12, 1.94)	0.290
Caloric soft drinks					
No. of cases	945	189	157	27	
Rate per 10,000 person-years	8.2	6.8	6.0	4.8	
Age-adjusted HR (95% CI)	1.0	0.96 (0.82, 1.12)	1.07 (0.90, 1.27)	1.08 (0.74, 1.59)	
Multivariable-adjusted HR (95% CI)					
Model 1‡	1.0	0.96 (0.82, 1.12)	1.04 (0.88, 1.24)	1.03 (0.70, 1.51)	
Model 2¥	1.0	0.97 (0.82, 1.14)	1.05 (0.88, 1.25)	0.95 (0.64, 1.43)	
Final model¤	1.0	0.98 (0.83, 1.15)	1.07 (0.89, 1.28)	0.98 (0.65, 1.46)	0.730

*Total person-time: 1,743.453 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. Models were reciprocally adjusted for the other sugar-sweetened beverage types. HR, hazard ratio; CI, confidence interval.

‡Model 1 adjusted for: age, race/ethnicity, socioeconomic status, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, diabetes, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use.

¥Model 2 adjusted for: Model 1 and body mass index, total energy intake, and dietary variables: red meat, processed meat, and vegetable intakes.

¤Final model: age, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, multivitamin use, menopausal status, menopausal hormone therapy use, body mass index, and total energy intake.

Supplemental Table 3.1: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	40,911	33,198	21,403	4,286
Age, y	55.4 ± 0.06	48.9 ± 0.07	48.8 ± 0.09	48.8 ± 0.20
Race/ethnicity, %				
Asian/PI	1,157 (2.8)	1,512 (4.6)	824 (3.9)	118 (2.8)
African-American	729 (1.8)	1,113 (3.4)	688 (3.2)	117 (2.7)
Hispanic/Latino	1,309 (3.2)	1,736 (5.2)	1,109 (5.2)	192 (4.5)
Native American	316 (0.8)	234 (0.7)	159 (0.7)	26 (0.6)
White	36,667 (89.6)	27,919 (84.1)	18,147 (84.8)	3,750 (87.5)
Other/Mixed	428 (1.1)	450 (1.4)	302 (1.4)	55 (1.3)
Unknown	305 (0.8)	234 (0.7)	188 (0.9)	28 (0.7)
Education, % ǂ				
Academic doctorate	795 (1.9)	557 (1.7)	365 (1.7)	94 (2.2)
Professional doctorate	217 (0.5)	162 (0.5)	129 (0.6)	26 (0.6)
Master's degree	10,494 (25.7)	8,934 (26.9)	5,686 (26.6)	1,150 (26.8)
Bachelor's degree	9,112 (22.3)	7,746 (23.3)	4,518 (21.1)	868 (20.3)
Associate's degree	130 (0.3)	132 (0.4)	92 (0.4)	17 (0.4)
Technical school/certificate/High school	8 (0.0)	6 (0.0)	8 (0.0)	4 (0.1)
Less than High school	0	1 (0)	0	0
Unknown	20,155 (49.3)	15,660 (47.2)	10,605 (49.6)	2,127 (49.6)
Occupation, %				
Teacher, single grade Pre-K to High school	17,994 (44.0)	18,551 (55.9)	12,149 (56.8)	2,475 (58.8)
Teacher, other	2,885 (7.1)	2,478 (7.5)	1,636 (7.6)	364 (8.5)
Multiple	193 (0.5)	251 (0.8)	147 (0.7)	30 (0.7)
Pupil Services	1,146 (2.8)	1,099 (3.3)	690 (3.2)	136 (3.2)
Administration	1,311 (3.2)	1,221 (3.7)	866 (4.1)	198 (4.6)
Teacher, Pre-K/Elem/Other or JrH/Hi/Other	270 (0.7)	284 (0.9)	183 (0.9)	42 (1.0)
Pupil Services/Admin or Pupil Services/Admin/Teacher	400 (1.0)	351 (1.1)	241 (1.1)	43 (1.0)
Unknown	16,712 (40.9)	8,963 (27.0)	5,491 (25.7)	1,080 (24.0)
Socioeconomic status, %				
1st quartile, low	1,614 (4.0)	1,493 (4.5)	959 (4.5)	177 (4.1)
2nd quartile, low-medium	6,728 (16.5)	5,846 (17.6)	3,835 (17.9)	718 (16.8)
3rd quartile, medium-high	13,030 (31.9)	11,072 (33.4)	6,891 (32.2)	1,436 (33.5)
4th quartile, high	19,017 (46.5)	14,328 (43.2)	9,435 (44.1)	1,904 (44.4)
Unknown	522 (1.3)	459 (1.4)	283 (1.3)	51 (1.2)
Marital status, %				
Married	18,457 (45.1)	16,268 (49.0)	10,016 (46.8)	1,973 (46.0)
Divorced	3,547 (8.7)	2,688 (8.1)	1,637 (7.7)	359 (8.4)
Separated	284 (0.7)	289 (0.9)	188 (0.9)	33 (0.8)
Widowed	3,346 (8.2)	1,558 (4.7)	999 (4.7)	178 (4.2)
Never married	1,974 (4.8)	1,685 (5.1)	1,079 (5.0)	2761(6.1)
Unknown	13,303 (32.5)	10,710 (32.3)	7,484 (35.0)	1,482 (34.6)
Dietary Intake				
Energy, kcal/day	1755.3 ± 3.35	1954.4 ± 3.72	2046.5 ± 4.64	2255.4 ± 10.36
Carbohydrate, g/day	251.5 ± 0.18	253.4 ± 0.20	260.2 ± 0.25	282.6 ± 0.55
Protein, g/day	80.6 ± 0.07	76.8 ± 0.07	74.4 ± 0.09	68.0 ± 0.20
Total Fat, g/day	60.0 ± 0.07	61.6 ± 0.07	59.8 ± 0.09	53.7 ± 0.20
Fruit & Vegetables, g/day	359.7 ± 0.87	299.9 ± 0.96	285.6 ± 1.19	266.1 ± 2.67
Vegetables, g/day	183.8 ± 0.54	163.4 ± 0.60	163.4 ± 0.75	167.7 ± 1.67
Red meat, g/day	29.4 ± 0.17	34.7 ± 0.19	36.1 ± 0.23	37.3 ± 0.52
Processed meat intake, g/day	6.5 ± 0.06	8.2 ± 0.06	8.5 ± 0.08	8.9 ± 0.18
Total dairy intake, g/day	224.1 ± 0.98	224.1 ± 1.09	215.6 ± 1.36	212.9 ± 3.04
Dietary folate intake, g/day	420.0 ± 0.81	436.4 ± 0.90	438.6 ± 1.12	442.5 ± 2.50
SSB intake, fl oz	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.5 ± 0.05
MVPA, minutes/week	236.3 ± 1.22	213.7 ± 1.35	219.5 ± 1.68	220.7 ± 3.76
Smoking, %				
Never	25,837 (63.2)	23,304 (70.2)	14,680 (68.6)	2,785 (65.0)
Former	12,942 (31.6)	8,375 (25.2)	5,597 (26.2)	1,175 (27.4)
Current	2,084 (5.1)	1,494 (4.5)	1,100 (5.1)	321 (7.5)
Unknown	48 (0.1)	25 (0.1)	26 (0.1)	5 (0.1)
Number of cigarettes per day, ¥	13.3 ± 0.08	11.5 ± 0.10	12.1 ± 0.13	14.4 ± 0.27
Total smoke years, ¥	21.1 ± 0.11	17.8 ± 0.14	18.4 ± 0.17	20.0 ± 0.36

Supplemental Table 3.1: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*, Continued

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
Alcohol consumption, %				
None	13,950 (34.1)	10,513 (31.7)	6,983 (32.6)	1,636 (38.2)
<20 g/day	23,005 (56.2)	20,308 (61.2)	12,818 (59.9)	2,328 (54.3)
≥20 g/day	3,956 (9.7)	2,377 (7.2)	1,602 (7.5)	322 (7.5)
Body mass index, kg/m^2	24.9 ± 0.03	24.6 ± 0.03	25.0 ± 0.04	25.7 ± 0.08
Body mass index, kg/m^2				
Underweight, <18.5	982 (2.4)	888 (2.7)	543 (2.5)	116 (2.7)
Normal, 18.5-24.9	22,710 (55.5)	19,468 (58.6)	12,088 (56.5)	2,203 (51.4)
Overweight, 25-29.9	10,052 (24.6)	7,619 (23.0)	5,060 (23.6)	1,054 (24.6)
Obese, ≥30	5,487 (13.4)	4,217 (12.7)	3,079 (14.4)	787 (18.4)
Unknown	1,680 (4.1)	1,006 (3.0)	633 (3.0)	126 (2.9)
Hypertension, %	7,842 (19.2)	4,288 (12.9)	3,022 (14.1)	673 (15.7)
Diabetes, %	1,712 (4.2)	434 (1.3)	344 (1.6)	109 (2.5)
Aspirin use, %				
Daily	3,656 (8.9)	1,736 (5.2)	1,231 (5.8)	294 (6.9)
Up to 6x/week	5,770 (14.1)	4,806 (14.5)	3,154 (14.7)	684 (16.0)
Regular use, unknown frequency	258 (0.6)	171 (0.5)	145 (0.7)	21 (0.5)
Not regularly taken	30,652 (74.9)	26,075 (78.5)	16,604 (77.6)	3,233 (75.4)
Unknown use	575 (1.4)	410 (1.2)	269 (1.3)	54 (1.3)
Antihypertensive medication use, at least 1 medication, %				
Daily	7,201 (17.6)	3,679 (11.1)	2,622 (12.3)	599 (14.0)
Up to 6x/week	566 (1.4)	404 (1.2)	267 (1.3)	75 (1.8)
Regular use, unknown frequency	525 (1.3)	292 (0.9)	209 (1.0)	39 (0.9)
Not regularly taken	32,044 (78.3)	28,414 (85.6)	18,036 (84.3)	3,519 (82.1)
Unknown use	575 (1.4)	409 (1.2)	269 (1.3)	54 (1.3)
Multivitamin use, %				
Daily	16,355 (40.0)	10,578 (31.9)	6,930 (32.4)	1,492 (34.8)
Up to 6x/week	5,928 (14.5)	6,748 (20.3)	3,983 (18.6)	659 (15.4)
Never	6,559 (16.0)	5,252 (15.8)	3,430 (16.0)	695 (16.2)
Unknown use	12,069 (29.5)	10,620 (32.0)	7,060 (33.0)	1,440 (33.6)
Cancer family history, % ¤	22,250 (54.4)	17,160 (51.7)	11,083 (51.8)	2,257 (52.7)
Colorectum cancer family history, % §	3,791 (9.3)	2,562 (7.7)	1,711 (8.0)	312 (7.3)
Menopausal status and menopausal HT use, %				
Premenopausal	13,084 (32.0)	16,777 (50.5)	10,722 (50.1)	2,098 (49.0)
PP, no HT	5,639 (13.8)	2,879 (8.7)	1,913 (8.9)	380 (8.9)
PP, past HT	3,241 (7.9)	1,620 (4.9)	1,038 (4.9)	214 (5.0)
PP, current HT Estrogen	6,287 (15.4)	3,567(10.7)	2,257 (10.6)	480 (11.2)
PP, current HT Estrogen & Progesterone	7,128 (17.4)	4,335 (13.1)	2,739 (12.8)	510 (11.9)
All other	5,532 (13.5)	4,020 (12.1)	2,734 (12.8)	604 (14.1)
Oral contraceptive use, %				
Current	1,528 (3.9)	2,435 (7.6)	1,520 (7.4)	315 (7.6)
Past	22,996 (58.4)	21,194 (65.8)	13,860 (67.0)	2,782 (67.5)
Never	14,798 (37.6)	8,497 (26.4)	5,262 (25.4)	1,013 (24.6)
Unknown if current or past	71 (0.2)	72 (0.2)	47 (0.2)	12 (0.3)

*Values are n (%) for categorical variables and means ± SEMs for continuous variables. ǂEducation was obtained after baseline, during fourth mail-in questionnaire follow-up, 2005-2006. ¥Former of current smokers. ¤Cancer family history includes breast, endometrial, ovarian, cervical, lung, thyroid, colon, rectal, prostate, melanoma, and skin cancers, and also leukemia, and Hodgkin's lymphoma history, of first-degree relatives (parent, sibling, offspring). §Colorectum cancer family history includes disease in first-degree relatives (parent, sibling, offspring). Elem indicates Elementary; fl oz, fluid ounces; g/day, grams per day; Hi, High School; HT, hormone therapy; JrH, Junior High School; kcal/day, kilocalories per day; mo, months; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; Pre-K, pre-kindergarten; SSB, sugar-sweetened beverage; y, years.

Supplemental Table 3.2: Colorectal Cancer Risk* According to Sugar-Sweetened Beverage Consumption in Cups per Day

	Sugar-Sweetened Beverage Consumption †					
Colorectal Cancer	Rare or never	Up to ½ cup/day	Up to 1 cup/day	Up to 1 ½ cups/day	>1 ½ cups/day	P trend
Total						
No. of cases	663	436	102	60	57	
Rate per 10,000 person-years	9.5	6.7	5.4	6.5	5.2	
Age-adjusted HR (95% CI)	1.0	0.96 (0.85, 1.09)	0.89 (0.72, 1.10)	1.15 (0.88, 1.50)	1.04 (0.79, 1.37)	
Multivariable-adjusted HR (95% CI)						
Model 1ǂ	1.0	0.97 (0.86, 1.09)	0.88 (0.71, 1.09)	1.14 (0.87, 1.49)	1.01 (0.77, 1.33)	
Model 2¥	1.0	0.98 (0.86, 1.11)	0.88 (0.71, 1.09)	1.13 (0.86, 1.50)	0.97 (0.73, 1.30)	
Final Model¤	1.0	0.98 (0.86, 1.11)	0.88 (0.71, 1.10)	1.13 (0.86, 1.49)	0.99 (0.74, 1.31)	0.981
Proximal Colon						
No. of cases	375	228	55	32	28	
Rate per 10,000 person-years	5.4	3.5	2.9	3.4	2.5	
Age-adjusted HR (95% CI)	1.0	0.94 (0.79, 1.11)	0.92 (0.69, 1.22)	1.19 (0.83, 1.72)	1.04 (0.70, 1.53)	
Multivariable-adjusted HR (95% CI)						
Model 1ǂ	1.0	0.95 (0.80, 1.12)	0.92 (0.69, 1.23)	1.20 (0.83, 1.72)	1.03 (0.70, 1.53)	
Model 2¥	1.0	0.97 (0.82, 1.16)	0.92 (0.68, 1.24)	1.20 (0.82, 1.76)	1.01 (0.67, 1.52)	
Final Model¤	1.0	0.96 (0.80, 1.14)	0.89 (0.66, 1.21)	1.17 (0.80, 1.71)	0.97 (0.64, 1.46)	0.945
Distal Colorectum						
No. of cases	288	208	47	28	29	
Rate per 10,000 person-years	4.1	3.2	2.5	3.0	2.6	
Age-adjusted HR (95% CI)	1.0	0.99 (0.82, 1.18)	0.85 (0.62, 1.16)	1.10 (0.74, 1.62)	1.05 (0.71, 1.54)	
Multivariable-adjusted HR (95% CI)						
Model 1ǂ	1.0	0.99 (0.83, 1.19)	0.84 (0.61, 1.15)	1.08 (0.73, 1.59)	0.98 (0.67, 1.45)	
Model 2¥	1.0	0.99 (0.82, 1.19)	0.84 (0.61, 1.16)	1.06 (0.71, 1.59)	0.94 (0.63, 1.41)	
Final Model¤	1.0	1.00 (0.83, 1.21)	0.87 (0.63, 1.20)	1.09 (0.73, 1.64)	1.00 (0.67, 1.50)	0.912

*Total person-time: 1,743.453 years. HR, hazard ratio; CI, confidence interval.

ǂModel 1 adjusted for: age, race/ethnicity, socioeconomic status, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, diabetes, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use.

¥Model 2 adjusted for: Model 1 and body mass index, total energy intake, and dietary variables: red meat, processed meat, and vegetable intakes.

¤Final model: age, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, multivitamin use, menopausal status, menopausal hormone therapy use, body mass index, and total energy intake.

Supplemental Table 3.3: Colorectal Cancer Risk* According to Sugar-Sweetened Beverage Consumption after removal of events that occurred at 2 years follow-up (n=97,776)

	Sugar-Sweetened Beverage Consumption				
Colorectal Cancer	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Total					
No. of cases	596	330	232	50	
Rate per 10,000 person-years	8.6	5.6	6.1	6.6	
Age-adjusted HR (95% CI)	1.0	0.93 (0.82, 1.07)	1.05 (0.90, 1.23)	1.18 (0.88, 1.57)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.93 (0.81, 1.07)	1.04 (0.89, 1.21)	1.16 (0.87, 1.55)	
Model 2[¥]	1.0	0.93 (0.81, 1.08)	1.06 (0.91, 1.25)	1.16 (0.86, 1.57)	
Final Model[¤]	1.0	0.94 (0.82, 1.09)	1.07 (0.91, 1.25)	1.16 (0.86, 1.56)	0.187
Proximal Colon					
No. of cases	345	180	114	25	
Rate per 10,000 person-years	5.0	3.0	3.0	3.3	
Age-adjusted HR (95% CI)	1.0	0.94 (0.78, 1.13)	0.96 (0.78, 1.19)	1.12 (0.74, 1.68)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.95 (0.79, 1.14)	0.96 (0.78, 1.20)	1.11 (0.74, 1.67)	
Model 2[¥]	1.0	0.97 (0.80, 1.17)	0.98 (0.78, 1.23)	1.11 (0.73, 1.69)	
Final Model[¤]	1.0	0.95 (0.79, 1.15)	0.97 (0.78, 1.21)	1.11 (0.73, 1.68)	0.799
Distal Colorectum					
No. of cases	251	150	118	25	
Rate per 10,000 person-years	3.6	2.5	3.1	3.3	
Age-adjusted HR (95% CI)	1.0	0.93 (0.76, 1.14)	1.16 (0.93, 1.45)	1.25 (0.83, 1.89)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.91 (0.74, 1.12)	1.13 (0.90, 1.41)	1.22 (0.81, 1.85)	
Model 2[¥]	1.0	0.90 (0.73, 1.12)	1.17 (0.93, 1.47)	1.23 (0.80, 1.89)	
Final Model[¤]	1.0	0.93 (0.75, 1.15)	1.19 (0.95, 1.49)	1.22 (0.80, 1.86)	0.098

*Total person-time: 1,741,103 years. HR indicates hazard ratio; CI, confidence interval.

[ǂ]Model 1 adjusted for: age, race/ethnicity, socioeconomic status, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, diabetes, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use.

[¥]Model 2 adjusted for: Model 1 and body mass index, total energy intake, and dietary variables: red meat, processed meat, and vegetable intakes.

[¤]Final model: age, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, multivitamin use, menopausal status, menopausal hormone therapy use, body mass index, and total energy intake.

Supplemental Table 3.4: Colorectal Cancer Risk* According to Sugar-Sweetened Beverage Consumption after removal of events that occurred at 4 years follow-up (n=95,667)

	Sugar-Sweetened Beverage Consumption				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Colorectal Cancer					
No. of cases	533	292	206	46	
Rate per 10,000 person-years	7.7	5.0	5.5	6.1	
Age-adjusted HR (95% CI)	1.0	0.91 (0.79, 1.05)	1.03 (0.87, 1.21)	1.19 (0.88, 1.61)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.91 (0.79, 1.05)	1.02 (0.87, 1.20)	1.17 (0.87, 1.59)	
Model 2[¥]	1.0	0.92 (0.79, 1.07)	1.06 (0.89, 1.26)	1.20 (0.87, 1.64)	
Final Model[¤]	1.0	0.92 (0.79, 1.07)	1.05 (0.89, 1.25)	1.17 (0.86, 1.59)	0.215
Proximal Colon					
No. of cases	317	164	103	23	
Rate per 10,000 person-years	4.6	2.8	2.7	3.0	
Age-adjusted HR (95% CI)	1.0	0.92 (0.76, 1.11)	0.93 (0.74, 1.17)	1.10 (0.72, 1.68)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.93 (0.76, 1.12)	0.93 (0.75, 1.17)	1.10 (0.72, 1.68)	
Model 2[¥]	1.0	0.95 (0.78, 1.16)	0.95 (0.75, 1.21)	1.11 (0.71, 1.72)	
Final Model[¤]	1.0	0.93 (0.77, 1.14)	0.93 (0.74, 1.18)	1.08 (0.70, 1.68)	0.994
Distal Colorectum					
No. of cases	216	128	103	23	
Rate per 10,000 person-years	3.1	2.2	2.7	3.0	
Age-adjusted HR (95% CI)	1.0	0.90 (0.72, 1.13)	1.15 (0.91, 1.46)	1.31 (0.85, 2.03)	
Multivariable-adjusted HR (95% CI)					
Model 1[ǂ]	1.0	0.89 (0.71, 1.12)	1.13 (0.89, 1.43)	1.27 (0.83, 1.97)	
Model 2[¥]	1.0	0.89 (0.71, 1.13)	1.20 (0.93, 1.53)	1.32 (0.84, 2.08)	
Final Model[¤]	1.0	0.91 (0.73, 1.15)	1.21 (0.95, 1.54)	1.28 (0.82, 1.99)	0.068

*Total person-time: 1,734,557 years. HR indicates hazard ratio; CI, confidence interval.

[ǂ]Model 1 adjusted for: age, race/ethnicity, socioeconomic status, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, diabetes, physical activity, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use.

[¥]Model 2 adjusted for: Model 1 and body mass index, total energy intake, and dietary variables: red meat, processed meat, and vegetable intakes.

[¤]Final model: age, total smoke years, alcohol intake, colorectum cancer family history of first-degree relatives, history of polyps, multivitamin use, menopausal status, menopausal hormone therapy use, body mass index, and total energy intake.

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CHAPTER 4:

SUGAR-SWEETENED BEVERAGE INTAKE AND ALL-CAUSE, CARDIOVASCULAR DISEASE- AND CANCER-SPECIFIC MORTALITY IN THE CALIFORNIA TEACHERS STUDY

ABSTRACT

Background: The association between sugar-sweetened beverage (SSB) consumption and mortality risk has been limited and published data are inconsistent.

Methods: We examined the association of SSB consumption and mortality risk in 100,314 women free of CVD, cancer, and diabetes participating in the California Teachers Study, a United States-based longitudinal cohort of female teachers and administrators. SSBs were defined as caloric soft drinks, sweetened bottled waters and teas, and fruit drinks (other than fruit juices). Data was derived from a self-administered food frequency questionnaire (Block95) and quantities collapsed into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. Mortality was ascertained via annual linkage with state- and nationwide mortality files and national death index data. Cox proportional hazards models were used to assess the multivariable-adjusted association (hazard ratio [HR] and 95% confidence intervals [95% CI]) between SSB consumption and risk of mortality.

Results: A total of 14,143 deaths were documented over 20 years, of which 30.5% (n=4,313) were from cardiovascular disease and 29.2% (n=3,457) from cancer. Compared with rare/never consumers, the multivariable-adjusted HRs (95% CI) were 1.04 (95% CI 0.94, 1.15; [*P* trend = 0.75]) for all-cause; 1.03 (95% CI 0.84, 1.25)]; *P* trend = 0.74) for CVD-specific; and 1.07 (95% CI 0.90, 1.26, *P* trend = 0.67) for cancer-specific mortality among women who

consumed ≥ 1 serving/day of SSBs. Significant increased multivariable-adjusted HRs [95% CI] were observed for all-cause mortality (1.30 [1.14, 1.48]; *P* trend = 0.002) and cancer-specific mortality (1.38 [1.13, 1.69]; *P* trend = 0.029) in women who consumed ≥1 serving/day of caloric soft drink compared to rare/never consumers.

Conclusion: SSBs were not significantly associated with mortality risk, though a non-significant modest association was suggested. Regular consumption of caloric soft drinks was positively associated with a higher risk of all-cause and cancer-specific mortality, and showed a significant linear trend. Future research should examine intake of SSBs in large, racial/ethnically diverse cohorts of males and females and address changes in SSB consumption over time.

Introduction

Sugar-sweetened beverages (SSBs) are responsible for almost half of all added sugars consumed by Americans.[1] While the overall intake of SSBs in the United States (U.S.) considerably declined from 2003 to 2014,[2] recent data show that on any given day, 49.3% of U.S. adults consume at least one SSB.[3] These beverages include carbonated and noncarbonated manufactured drinks containing any kind of added caloric sweetener or syrup such as soft drinks, fruit drinks, sports and energy drinks, sweetened waters, and tea and coffee beverages.[1] Excess intake of added sugars from SSBs is effortless since, on average, a 12 fl oz serving of a soft drink contains 150 calories and 35g of sugar, while an 8 fl oz serving of sweetened tea or fruit drink contains 100 calories and 15g to 20g of sugar.[4]

There are national and international recommendations on added sugars and discretionary calories that provide guidance about SSB intake. In the U.S., the 2015–2020 Dietary Guidelines Advisory Committee[1] recommends added sugars consumption of <10% of total daily energy intake, however SSBs currently contribute, on average, 6.9% (~179 kcal) and 6.1% (~113 kcal) of total caloric intake in adult men and women, respectively, according to recent data from the National Health and Nutrition Examination Survey (2011-2014).[3]

Studies have shown an association between consumption of SSBs and an adverse cardiometabolic health profile including weight gain,[5–7] visceral adiposity,[8] obesity,[9–11] metabolic syndrome[12–14] and type 2 diabetes,[6,15–17] hypertension,[18–20] coronary heart disease,[21,22] and stroke,[23–26] among ethnically diverse populations. Although substantial work has addressed the association between SSBs and cardiometabolic risk factors and evidence on the association with cardiovascular disease (CVD) is emerging, there is a limited number of studies examining

the association between SSB intake and risk of mortality,[27–29] and those published have inconsistent findings.

We aim to examine the association between SSB consumption and risk of mortality, including all-cause, CVD-specific, and cancer-specific, in a large prospective U.S. cohort of adult women over a 20-year period. We hypothesized that higher levels of SSB consumption are associated with an increased mortality risk.

Methods

Study Population and Design

The California Teachers Study (CTS) is an ongoing prospective cohort study comprised of 133,477 active and retired female teachers and administrators and members of the California State Teachers Retirement System, who completed a mailed questionnaire at study enrollment in 1995–1996. Methodological details of the cohort have been previously published.[30] The baseline questionnaire was 16 pages and encompassed a comprehensive range of participant information including demographic and lifestyle characteristics, behavioral factors, family history of chronic disease, medical history and co-morbidities. Annual follow-up surveys are conducted to determine change of residence, cancer diagnoses, hospitalizations, ambulatory care procedures, and death. Change of residence is attained by mailings and participant communication. Cancer diagnoses are ascertained by linkage with the California Cancer Registry, a statewide population-based cancer registry where cancer diagnoses in California residents are reported. Linkage with the Office of Statewide Health Planning and Development (OSHPD) provides hospitalization and ambulatory care procedures and diagnoses performed in California. Date of and cause of death are determined using state and national mortality files and the National Death Index.

The CTS study was approved by the Institutional Review Boards at the City of Hope, the University of Southern California, the University of California San Francisco, and the University of California at Irvine. This analysis was approved by the Institutional Review Boards of City of Hope and the University of California San Diego.

Assessment of Sugar-Sweetened Beverage Intake

Dietary intake during the year prior to baseline was assessed using a validated 103-item self-administered FFQ, developed from a former version of the Block 95 FFQ. We determined usual serving size (i.e., small medium, large or extra-large serving) and frequency of consumption (i.e., never or <1 time/month, 1 time/month, 2–3 times/month, 1 time/week, 2 times/week, 3–4 times/week, 5–6 times/week, every day, and/or ≥2 times/day) for the 103 food and beverage items. The reproducibility and validity of this instrument in the cohort has been previously described.[31]

SSB consumption was estimated by a composite of sweetened carbonated and noncarbonated beverages, including caloric soft drinks, sweetened bottled waters and/or teas, and fruit drinks (other than fruit juice), derived from 3 items on the FFQ: 'Regular soft drinks (not diet soda)', 'Snapple, Calistoga, sweetened bottled waters or iced teas', and 'Kool-Aid, Hi-C, or other drinks with added Vitamin C', respectively. From the 9 possible frequency categories ranging from 'never or less than once per month' to '≥2 times/day', SSB consumption was collapsed into four categories: Rare or never, >rare/never to <1 serving/week, ≥1 serving/week to <1 serving/day, and ≥1 serving/day. A serving of SSB was defined as 8 fluid ounces (fl oz), approximate weight 237 grams, for sweetened bottled water and/or teas and fruit drinks, and 12 fl oz, approximate weight 355 grams, for caloric soft drinks.

Ascertainment of Death

Deaths were identified from annual linkage with California mortality files, the Social Security Death Index, and the National Death Index records through December 31, 2015, providing mortality data that included underlying cause of death. Participants not matched with a death record were considered alive during the follow-up period. Using the International

Classification of Diseases (ICD) 9th and 10th Revision codes, study endpoints were defined as follows: (1) all-cause mortality; (2) CVD-specific mortality (ICD-9 codes 390-398, 402, 404, 410-429, and 430-438 and ICD-10 codes I00 to I09, I11, I13, and I20 to I51, I60 to I69) that includes diseases of the heart, hypertension, atherosclerosis, and cerebrovascular diseases; (3) heart disease-specific mortality (ICD-9 codes 390-398, 402, 404, 410-429 and ICD-10 codes I00 to I09, I11, I13, and I20 to I51); (4) cerebrovascular disease-specific mortality (ICD-9 codes 430-438 and ICD-10 codes I60 to I69); (5) cancer-specific mortality (ICD-9 codes 140-209 and ICD-10 codes C00 to C97), which only includes malignant neoplasms, excluding in situ and benign neoplasms; (6) breast cancer-specific mortality (ICD-9 code 1749 and ICD-10 code C509); (7) lung cancer-specific mortality (ICD-9 code 162 and ICD-10 code C34); and 8) colorectal cancer-specific mortality (ICD-9 codes 153, 154 and ICD-10 codes C18-C20). Participants were followed from completion of baseline questionnaire, corresponding to study start date, until death or end of follow-up (31 December 2015).

Assessment of Covariates

Self-reported demographic and clinical characteristics were collected at baseline as part of enrollment questionnaire and considered as possible confounders. Covariates included age, race, socioeconomic status (SES), marital status, smoking status, alcohol intake, family histories of CVD (includes myocardial infarction and/or cerebrovascular disease family histories),

diabetes, and cancer (includes breast, endometrial, ovarian, cervical, lung, thyroid, colon, rectal, prostate, melanoma, skin cancers, leukemia, and Hodgkin's lymphoma family histories) of first degree relatives (parent, sibling, offspring), moderate to vigorous physical activity (MVPA), aspirin frequency and duration, multivitamin frequency and duration, antihypertensive medication frequency and duration (of at least one), hypertension, menopausal status and menopausal hormone therapy use, oral contraceptive use, BMI, total energy intake, and set of dietary intake covariates.

SES was determined by combining three 1990 U.S. block census data variables (occupation, education, and family income); where all block groups in the state were ranked by occupation (% adults employed in managerial/professional occupation), level of education (% of adults over the age of 25 completing at least a college degree), and median family income, corresponding to quartiles analogous the statewide adult population. A summary score was developed for SES with categories ranging from 1 (lowest) to 4 (highest). Smoking status was derived from three questionnaire items addressing cumulative (lifetime) smoking exposure, age when first and last smoked, and average number of cigarettes currently or previously smoked. Alcohol intake was determined from frequency and number of drinks per week of beer, champagne and/or wine, and cocktails and/or liquor. Physical activity, including MVPA, was estimated using questionnaire-derived intensity, duration, and frequency of listed activities, on an average day. BMI (kg/m^2) was calculated as weight (kg) divided by height squared (m^2), from self-reported weight and height measurements.

Analytic Sample

We excluded participants who specified their data only be used for breast cancer research (n=22), returned incomplete or incomprehensible questionnaires (n=4), those with a

perinatal or neonatal death code (n=1), those with a history of cardiovascular disease at or before baseline - that is, myocardial infarction, cerebrovascular disease, and revascularization procedures such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) or percutaneous transluminal coronary angioplasty (PTCA) (n=3,851), history of cancer at or before baseline (n=14,126), history of diabetes at or before baseline (n=2,912), were age ≥ 85 years at baseline (n=1,693), had extreme caloric intake values (<600 [n=9,029] or >5000 [n=490] kcal/d) or had incomplete food frequency questionnaire (FFQ) data at baseline including vitamin use (n=1), those with a with a missing death code and label (n=632) or undefined death code (n=402), yielding a final analytic sample of 100,314 female participants for follow-up (Figure 4.1).

Statistical Analyses

Mean and standard error of mean (SEM) or proportion and frequency were calculated for baseline characteristics of cohort participants in each SSB consumption category. Cox proportional hazard modeling was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of all and cause-specific mortality risk according to SSB consumption. The independent, SSB type-specific associations between sweetened bottled water and/or tea, fruit drink, and caloric soft drink consumption and risk of all and cause-specific mortality were also examined. A median method was used to examine the linear trend across intake categories, whereby the median intake value of SSB in each category was designated to all individuals in that category. The statistical significance of the linear trend was tested by Cox proportional hazard model using the median intake value as a continuous independent variable. The proportional hazards assumption was met by inspecting the survival curves according to SSB consumption categories as well as testing time-varying covariates in the model.

For the multivariate analysis, we adjusted for these potential confounders: age, race (White, Asian/Pacific Islander, African-American, Hispanic, Native-American, or Mixed/Other; further categorized as White vs all other), SES (quartiles: 1st, 2nd, 3rd, 4th, or unknown), marital status (married, separated/divorced, widowed, or all other), smoking status (never, past, current cigarette use [1–12, 13–24, ≥25/day], or unknown use), alcohol intake (0, <20, or ≥20 grams/day), family history of CVD (yes or no), family history of cancer (yes or no), family history of diabetes (yes or no), MVPA (quintiles min/week: 0-30, 30-105, 105-210, 210-360, >360, and unknown), aspirin use (did not take regularly, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency, or unknown), multivitamin use (never, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency), use of at least one antihypertensive medication (did not take regularly, 1-3 times/week, 4-6 times/week, daily, regular use but undetermined frequency, or unknown), hypertension (yes or no), menopausal status and menopausal hormone therapy use (premenopausal, perimenopausal/postmenopausal with never, past, or current hormone therapy use of estrogen, estrogen & progesterone, or other hormone combinations), and oral contraceptive use (never, past or current). We further adjusted for possible mediators BMI, total energy intake, and a set of dietary intake covariates: red meat, processed meat, and non-starchy vegetables. Intake of these three diet components were adjusted for total energy by using the residual method,[32] before including them in the model.

A total of three progressively adjusted multivariable Cox regression models were fitted after the age-adjusted model. Model 1 included sociodemographic characteristics and cardiometabolic and cancer risk factors. Model 2 additionally adjusted for BMI, total energy intake, and intake red and processed meat and non-starchy vegetables. The final model is the parsimonious model, keeping a robust set of covariates that were known and tested (if ≥10%

change in HR) confounders in this exposure and outcome association. Variables with a p-value ≤0.05 remained in the final model. Additionally, the models examining the association between sweetened bottled waters and/or tea, fruit drink, and caloric soft drink consumption and risk of mortality, were reciprocally adjusted for the other beverage types (i.e. the sweetened water or tea analysis was adjusted for fruit drink and caloric soft drink, and vice versa).

Sensitivity analysis was conducted to further assess dose consumption and enhance intake resolution that could be lost with a semi-quantitative categorization. This included categorization of SSB intake in cups/day (1 cup = 8 fl oz) as: rare/never, up to ½ cup/day, up to 1 cup/day, up to 1 ½ cups/day, and ≥1 ½ cups/day. We also examined the possibility of reverse causality by excluding deaths that occurred within the first 2 and 4 years of follow-up. This also addressed potential confounding in the association between SSB and mortality risk, including all and cause-specific. All *P* values presented are from 2-tailed analyses; $P < 0.05$ was considered statistically significant. Analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Mortality Statistics: Total Cohort

A total of 27,303 deaths, with a 118.3 per 10,000 person-years age-adjusted mortality rate, were documented during 20 years follow-up. Deaths from circulatory system diseases (49.1 per 10,000 person-years), neoplasms (27.7 per 10,000 person-years), and nervous system diseases (10.9 per 10,000 person-years) were the top three leading causes of death in the cohort (Supplemental Table 4.1).

Age-adjusted mortality rate among non-White women was 1.4, 3.0, 1.4, and 3.2 per 10,000 person-years for Asian-Pacific Islanders, African-Americans, Hispanic/Latinos, and

Native-Americans, respectively (Supplemental Table 4.2). The greatest number of deaths was observed in women with a Bachelor's degree (12.8 per 10,000 person-years), followed by Master's degree (9.4 per 10,000 person-years), among participants that reported education attainment. The greatest mortality rate was observed in participants in the 4th SES quartile (42.6 per 10,000 person-years), followed by women in the 3rd SES quartile (33.4 per 10,000 person-years).

Mortality Statistics: Analytic Sample

A total of 14,143 deaths, with a 96.8 per 10,000 person-years age-adjusted mortality rate, were documented during 20 years follow-up. Deaths from circulatory system diseases (39.0 per 10,000 person-years), neoplasms (21.7 per 10,000 person-years), and nervous system diseases (10.1 per 10,000 person-years) were the top three leading causes of death in the cohort (Supplemental Table 4.3).

Age-adjusted mortality rate among non-White women was 1.0, 2.5, 1.1, and 1.8 per 10,000 person-years for Asian-Pacific Islanders, African-Americans, Hispanic/Latinos, and Native-Americans, respectively (Supplemental Table 4.4). The greatest number of deaths was observed in women with a Bachelor's degree (13.3 per 10,000 person-years), followed by Master's degree (9.6 per 10,000 person-years), among participants that reported education attainment. The greatest mortality rate was observed in participants in the 4th SES quartile (36.0 per 10,000 person-years), followed by women in the 3rd SES quartile (27.6 per 10,000 person-years).

Sugar-Sweetened Beverage and Mortality

During 20 years of follow-up (1,897,745 person-years), 14,143 participants died of all causes, of which 30.5% (n=4,313) were CVD-specific deaths (n=3,184 heart disease-specific

and n=1,129 cerebrovascular disease-specific deaths), and 29.2% (n=4,127) were cancer-specific deaths. Table 4.1 shows baseline demographic and lifestyle characteristics for participants according to SSB consumption. Among all participants, 4.3% consumed ≥1 serving/day of SSB (SSB daily consumers) whereas 40.5% of participants reported rarely/never consumed SSBs.

SSB daily consumers had an average (mean ± SEM) SSB daily intake of 13.6 ± 0.05 fl oz, and tended to have higher intake of total energy, carbohydrate, and red and processed meat, and lower intake of protein, fat, and fruit and vegetables compared to the rare/never consumers. They were also more likely to be younger, past or current smokers (34.8%), past or current OC users (72.8%), and had the highest overweight and obesity rates (41.9%). Consumption of sweetened bottled water and/or tea, fruit drink, and caloric soft drink among SSB daily consumers was 4.4%, 0.5% and 3.2%, respectively. Comprehensive participant characteristics are reported in Supplemental Table 4.5.

Table 4.2 presents HRs for all-cause and cause-specific mortality according to semi-quantitative SSB consumption status. The HR (95% CI) for all-cause mortality and SSB consumption was 1.04 (0.94, 1.15) comparing women who consumed ≥1 serving/day of SSBs versus rare/never consumers (Final model, Table 4.2). The HR for CVD-specific mortality was lower (HR = 1.03 [95% CI 0.84, 1.25]) than that for cancer-specific mortality (HR = 1.07 [95% CI 0.90, 1.26]) in the final multivariable-adjusted model. The trend test did not show linearity in any of the associations (all *P* trend >0.05). There was no significant association between SSB intake and mortality after taking into account potential confounders including sociodemographic, cardiometabolic and cancer risk factors (Model 1), BMI, and dietary intake (Model 2) (Table 4.2).

With regards to type of SSB, we observed an association between caloric soft drink consumption and risk of all-cause and cancer-specific mortality (Table 4.4). Women who consumed ≥1 serving/day of caloric soft drink, had a 30% increased risk of all-cause mortality (HR = 1.30 [95% CI: 1.14, 1.48; *P* trend = 0.002]) versus those who were rare/never consumers. Similarly, compared to the rare/never consumers of caloric soft drinks, the intake of ≥1 serving/day increased the risk cancer-specific mortality by 38% (HR = 1.38 [95% CI: 1.13, 1.69; *P* trend = 0.029]). Sweetened bottled waters and/or teas consumption was not associated with mortality.

Sensitivity analysis addressing SSB intake in cups/day, a statistically significant association between SSB intake and all-cause and cerebrovascular disease-specific mortality was observed (Supplemental Table 4.6). Women who consumed >1 ½ cups/day SSBs had a 17% higher risk of all-cause mortality (HR = 1.17 [95% CI: 1.06, 1.28]; *P* trend < 0.001) compared to rarely/never consumers (Model 1, Supplemental Table 4.6). In the final model, the association attenuated, yet a 15% higher risk of all-cause mortality (HR = 1.15 [95% CI: 1.04, 1.26]; *P* trend = 0.001), was observed among women who consumed >1 ½ cups/day SSBs, compared to rarely/never consumers. There was no association between SSB consumption and CVD-specific and cancer-specific mortality, however the risk of cerebrovascular disease-specific mortality increased by 47% (HR = 1.47 [95% CI: 1.04, 2.08]; *P* trend = 0.09) among those who had a SSB intake of >1 ½ cups/day, compared to rarely/never consumers (Final models, Supplemental Table 4.6).

Sensitivity analyses excluded events which occurred during the first 2 and 4 years of follow-up using both semi-quantitative and cups/day categorization schemes. The associations observed in the main analysis persisted after these exclusions (Supplementary Table 4.7 - 4.12).

Discussion

In this prospective cohort of U.S. women, SSBs were not significantly associated with mortality risk. A statistically significant positive association was observed between daily caloric soft drink consumption and risk of all-cause and cancer-specific mortality after covariate adjustment, suggesting that the type of SSB is influential in mortality risk, especially for cancer-specific related deaths. In sensitivity analysis, we observed a significant, dose-dependent positive association between consumption of >1 ½ cups/day of SSBs and risk of all-cause mortality, after accounting for cardiometabolic, lifestyle, and dietary factors. We also found a greater risk of cerebrovascular disease-specific mortality with a SSB intake >1 ½ cups/day, suggesting that the all-cause mortality findings were driven by this association. These findings remained after removal of deaths 2 and 4 years after baseline.

We did not observe a significant association between SSB consumption and mortality. In contrast to our main analysis findings, results from the Nurses' Health Study[29] showed that women that had a SSB intake between 1 to 2 servings/day had a 14% greater risk (HR = 1.14 [95% CI: 1.08, 1.20]; *P* trend = <0.0001) of total mortality, compared to non-consumers.[29] Our finding of a 15% higher risk (HR = 1.15 [95% CI: 1.04, 1.26]; *P* trend = 0.001) of all-cause mortality among women consuming >1 ½ cups/day of SSBs, versus rarely/never consumers, in sensitivity analysis, is consistent with the direction and significance of the association of that of the Nurses' Health Study, however a direct comparison is unsuitable.

Additionally, contrary to the Nurses' Health Study[29] results, we did not find an association between SSB consumption and risk of CVD-specific mortality. Malik et al.,[29] found a positive association between SSB intake and CVD mortality, stronger in women than in men. Similarly, Yang et al.,[33] reported a significant relationship between added sugar consumption

(SSBs as major source) and a persistent increased risk for CVD-specific mortality in a nationally representative sample of adults.[33] However, in sensitivity analysis, we observed a 47% greater risk (HR = 1.47 [95% CI 1.04, 2.08]; *P* trend = 0.09) of cerebrovascular disease-specific mortality in women who consumed >1 cups/day of SSB versus rarely/never consumers, in the multivariable-adjusted model. Cerebrovascular disease-specific mortality in regards to SSB consumption is not well documented, restricting our ability to make comparisons.

In regards to specific SSBs, we found a positive and dose-dependent association between consumption of ≥1 serving/day of caloric soft drink and all-cause mortality (HR = 1.30 [95% CI: 1.14, 1.48]; *P* trend = .002) when compared to rarely/never consumers. In contrast to our results, the Leisure World Cohort Study[28] and the Singapore Chinese Health Study,[27] examining regular cola and non-cola soft drink intake and mortality risk in Californian older adults and Chinese adults in Singapore respectively, found a null association between soft drink consumption and death, after adjusting for known confounders.[27,28] Consumption in these two studies was lower than in CTS, 3.2% in the Leisure World Cohort Study and 3.3% in the Singapore Chinese Health Study.

The majority of the published literature on SSB intake and CVD-related outcomes, has primarily ascertained incidence of a CVD event, including incidence of CHD and stroke (fatal and non-fatal)[23,24,26] with inconsistent findings among U.S., Swedish and Japanese populations and using distinct sweetened beverages (SSB composite versus soft drink intake), however cerebrovascular disease specific-mortality includes conditions in which ischemia or a hemorrhage affect the brain and/or surrounding cerebral blood vessels, encompassing more than stroke, such as stenosis and aneurysms. In our cohort, SSB consumption has been associated with risk of CVD as a composite of MI, revascularization, and stroke, in women that consumed

≥1 serving/day or >1 ½ cups/day SSBs, compared to rarely/never consumers. Risk of stroke among consumers of >1 ½ cups/day SSBs was 26% higher (HR = 1.26 [95% CI: 1.09, 1.46]) than rarely/never consumers of SSBs (data not shown).

Concerning cancer-specific mortality risk, we found a null association between SSB intake and death from total and type of cancer. The Singapore Chinese Health Study also saw a null association,[27] while Nurses' Health Study[29] data found a 16% higher risk of cancer-specific mortality risk in women consuming ≥2 servings/day of SSBs versus women consuming <1/month. A recent systematic review and meta-analysis found a null association between consumption of carbonated sweetened beverages and cancer risk (summary RR=1.03 [95% CI: 0.96; 1.11]). Authors also reported no independent association with pancreatic, bladder, kidney, squamous cell or adenocarcinoma of the esophagus, colon, gastric cardia, gastric non-cardia, prostate, breast, larynx, ovary, pharynx or glioma cancers.[34]

In regards to type of SSB and cancer, we found a 38% higher risk (HR = 1.38 [95% CI: 1.13, 1.69]; *P* trend = 0.029) of cancer-specific mortality risk in women who consume ≥1 serving/day of caloric soft drinks versus rare/never consumers. This finding is particularly interesting since we did not observe an association with SSB as a composite measure, yet caloric soft drink intake was strongly associated with death from cancer. Caloric soft drink intake and risk of colon and lymphoma and leukemia have reported null and discreet associations in pooled cohorts,[35,36] whereas the association with pancreatic risk has found to be strong (RR = 1.57 [95% CI: 1.02-2.41]; *P* trend = 0.05) in women consuming >3 caloric soft drinks per week versus <1 per month[37]; however a recently published findings for the Melbourne Collaborative Cohort Study, found that frequent consumption of caloric soft drinks

was associated with a larger waist circumference and a modest increase in obesity-related cancer risk, irrespective of participant's weight status.[38]

SSB consumption has been associated with adiposity[5,7,8] and detrimental chronic cardiometabolic disease and outcomes.[11,12,21,23] Thus, it is plausible that consumption of SSBs influences the risk of mortality through these intermediate conditions. Attenuation of the measure of association was observed after adjusting for common lifestyle factors including hypertension and obesity, suggesting these are risk factors in the association. Furthermore, we must not discount that SSB consumption may serve as a surrogate of a suboptimal diet and unhealthy lifestyle. Frequent consumption of SSBs is related with a Westernized dietary pattern, which is high in sodium, saturated fat, meat, and sugar, and low in fruit, vegetables, fiber, and wholegrain foods.[39–41]

Our study had several strengths. First, we had a large sample size and extended follow-up period. Second, we prospectively collected data on SSB consumption, dietary intake, and lifestyle characteristics, reduces the possibility of reverse causation and recall bias. Moreover, sensitivity analysis further addressed possibility of reverse causality. Third, collection of potential confounders to include as covariates in the multivariable model is another study strength. Fourth, efficient and comprehensive linkage to state- and nationwide records for mortality data acquisition, derived well-defined study outcomes without participant burden, while reducing bias due to loss to follow-up.

Regardless of these strengths, a limitation of the study is random measurement error since we only estimated SSB intake based on a single assessment at baseline. Another limitation is possible social desirability bias reporting dietary intake. Residual and unmeasured confounding should be recognized, since we could only adjust for covariates what were

collected. We could not address other beverages such as diet, low-calorie, and artificially sweetened beverages, since the FFQ used did not include these drinks. Our analyses could have benefited from further adjustment of cardiometabolic risk factors such as blood assay values for total and high-density lipoprotein cholesterol and measured systolic and diastolic blood pressure. In addition, we could not examine changes in SSB intake pattern over time. SSB consumption trends among U.S. adults has declined in recent years,[42,43] thus in respect to our results, we would foresee attenuation in the magnitude of the measure of association with current consumption shifts. Finally, generalizability is limited due to the homogeneous nature of the cohort being female and primarily non-Hispanic white.

Conclusions

In conclusion, in our sample of female teachers and administrators we found that daily consumption of at least 1 serving (12 fl oz) of caloric soft drink as associated with a higher risk of all-cause and cancer-specific mortality. In sensitivity analysis, daily consumption of >1 ½ cups of SSBs was associated with a higher risk in all-cause and cerebrovascular disease specific-mortality, after accounting for cardiometabolic and cancer risk factors, adiposity and dietary intake. Our findings add to the evidence of the negative effects of frequent SSBs consumption, underscoring the importance of limiting SSB intake to improve health and reduce mortality.

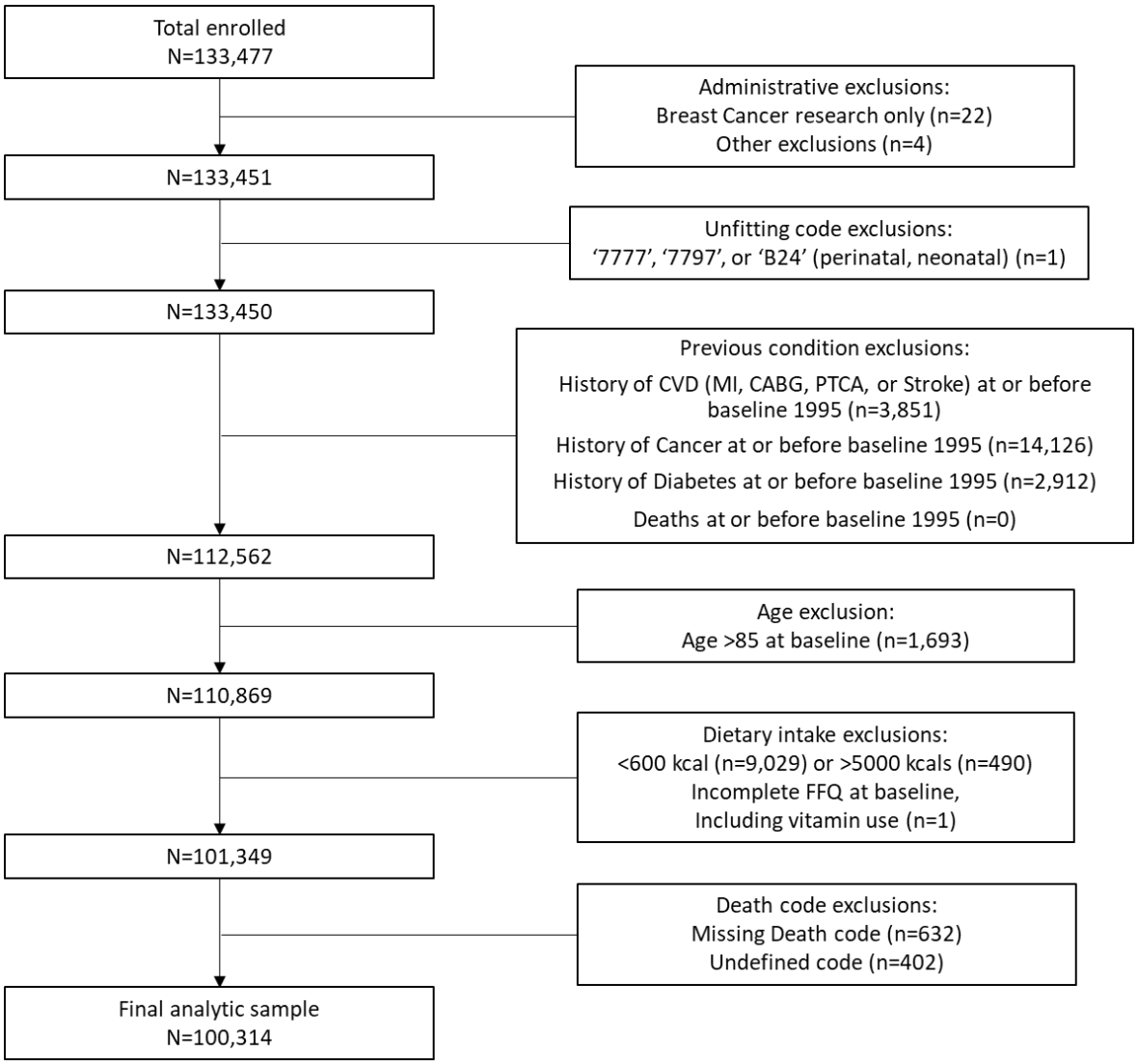

Figure 4.1: Flow-chart showing enrollment, exclusions and final analytic sample for sugar-sweetened beverage consumption and risk of mortality in the CTS.

Table 4.1: Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories[*] [†]

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	40,579	33,773	21,665	4,297
SSB intake, fl oz/day	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.6 ± 0.05
Dietary Intake				
Energy, kcal/day	1,756.6 ± 3.36	1,957.5 ± 3.68	2,047.7 ± 4.60	2,248.5 ± 10.32
Carbohydrate, g/day	252.2 ± 0.18	253.9 ± 0.19	260.4 ± 0.24	283.1 ± 0.54
Protein, g/day	80.4 ± 0.07	76.9 ± 0.07	74.5 ± 0.09	68.0 ± 0.20
Total Fat, g/day	59.9 ± 0.07	61.7 ± 0.07	60.0 ± 0.09	53.9 ± 0.20
Fruit and vegetable, g/day	359.6 ± 0.87	299.9 ± 0.94	285.1 ± 1.19	265.4 ± 2.66
Vegetables, g/day	183.9 ± 0.54	163.4 ± 0.59	163.3 ± 0.74	166.9 ± 1.66
Red meat, g/day	29.1 ± 0.17	34.7 ± 0.19	36.3 ± 0.23	36.8 ± 0.52
Processed meat intake, g/day	6.3 ± 0.06	8.2 ± 0.06	8.4 ± 0.08	8.7 ± 0.18
Age, y	55.3 ± 0.06	48.9 ± 0.07	48.8 ± 0.09	48.6 ± 0.20
Race/ethnicity, %				
White	36,568 (90.1)	28,531 (84.5)	18,471 (85.3)	3,774 (87.8)
All other	4,011 (9.9)	5,242 (15.5)	3,194 (14.7)	523 (12.2)
Education, % ǂ				
Academic/Professional doctorate	1,062 (2.6)	761 (2.3)	515 (2.4)	125 (2.9)
Master's degree	10,640 (26.2)	9,203 (27.3)	5,801 (26.8)	1,182 (27.5)
Bachelor's degree	9,167 (22.6)	7,906 (23.4)	4,612 (21.3)	874 (20.3)
Associate's degree or less	134 (0.3)	138 (0.4)	103 (0.5)	19 (0.4)
Unknown	19,576 (48.2)	15,765 (46.7)	10,634 (49.1)	2,097 (48.8)
Occupation, %				
Teacher, any kind	20,236 (49.9)	20,965 (62.1)	13,714 (63.3)	2,802 (65.2)
Pupil services	1,102 (2.7)	1,082 (3.2)	679 (3.1)	132 (3.1)
Administration	1,267 (3.1)	1,195 (3.5)	850 (3.9)	191 (4.4)
Any other combination	565 (1.4)	593 (1.8)	370 (1.7)	71 (1.7)
Unknown	17,409 (42.9)	9,938 (29.4)	6,052 (27.9)	1,101 (25.6)
Socioeconomic status, %				
1st quartile, low	1,422 (3.5)	1,421 (4.2)	914 (4.2)	168 (3.9)
2nd quartile, low-medium	6,124 (15.1)	5,628 (16.7)	3,671 (16.9)	684 (15.9)
3rd quartile, medium-high	12,044 (29.7)	10,736 (31.8)	6,639 (30.6)	1,366 (31.8)
4th quartile, high	17,791 (43.8)	13,905 (41.2)	9,107 (42.0)	1,814 (42.2)
Unknown	3,198 (7.9)	2,083 (6.2)	1,334 (6.2)	265 (6.2)
Marital status, %				
Married	18,668 (46.0)	16,701 (49.5)	10,234 (47.2)	1,995 (46.4)
Separated/Divorced	3,815 (9.4)	3,017 (8.9)	1,830 (8.5)	406 (9.5)
Widowed	3,327 (8.2)	1,579 (4.7)	1,011 (4.7)	182 (4.2)
All other	14,769 (36.4)	12,476 (36.9)	8,590 (39.7)	1,714 (39.9)
MVPA, minutes/week	240.4 ± 1.23	215.4 ± 1.35	221.7 ± 1.68	222.2 ± 3.78
Smoking, current, %	2,047 (5.0)	1,487 (4.4)	1,123 (5.2)	329 (7.7)
Alcohol consumption, ≥20 g/day, %	4,045 (10.0)	2,411 (7.1)	1,638 (7.8)	326 (7.8)
Obese, BMI ≥30 kg/m^2, %	5,015 (12.4)	4,145 (12.3)	2,993 (13.8)	752 (17.5)
Hypertension, %	7,042 (17.4)	4,134 (12.2)	2,885 (13.3)	616 (14.3)
Daily aspirin use, %	3,268 (8.1)	1,691 (5.0)	1,135 (5.2)	268 (6.2)
Daily antihypertensive medication use, %	6,444 (15.9)	3,562 (10.6)	2,504 (11.6)	547 (12.7)
Daily multivitamin use, %	16,244 (40.0)	10,777 (31.9)	7,035 (32.5)	1,495 (34.8)

Table 4.1: Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories[*] [†], Continued

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
Diabetes family history, % §	8,448 (20.8)	6,463 (19.1)	4,213 (19.5)	844 (19.6)
Cardiovascular disease family history, % ‖	20,804 (51.3)	14,991 (44.4)	9,726 (44.9)	1,970 (45.9)
Cancer family history, % #	22,060 (54.4)	17,511 (51.9)	11,246 (51.9)	2,283 (53.1)
Menopausal status and menopausal HT use, %				
Premenopausal	13,120 (32.3)	17,120 (50.7)	10,843 (50.1)	2,129 (49.6)
PP, no HT use	5,474 (13.5)	2,933 (8.7)	1,922 (8.9)	361 (8.4)
PP, past HT use	3,185 (7.9)	1,625 (4.8)	1,080 (5.0)	209 (4.9)
PP, current HT use, Estrogen	6,254 (15.4)	3,633 (10.8)	2,296 (10.6)	477 (11.1)
PP, current HT use, Estrogen & Progesterone	7,161 (17.7)	4,428 (13.1)	2,780 (12.8)	520 (12.1)
PP, all other HT combinations	5,385 (13.3)	4,034 (11.9)	2,744 (12.7)	601 (14.0)
Oral contraceptive use, past and current, %	24,578 (60.6)	24,049 (71.2)	15,567 (71.9)	3,130 (72.8)

*Values are means ± standard error mean or N (percentage). †1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Education was obtained after baseline, during fourth mail-in questionnaire follow-up (2005-2006). **§** Diabetes family history of first-degree relatives (parent, sibling, offspring). ‖ Cardiovascular disease family history includes heart attack/myocardial infarction and stroke family history of first-degree relatives (parent, sibling, offspring). **#** Cancer family history of first-degree relatives (parent, sibling, offspring). Fl oz indicates fluid ounces; g/day, grams per day; HT, hormone therapy; kcal/day, kilocalories per day; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; SSB, sugar-sweetened beverage; y, years.

Table 4.2: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories

	Sugar-Sweetened Beverage Consumption†				
Mortality	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-cause					
No. of cases	7,838	3,569	2,301	435	
Rate per 1,000 person-years	10.4	5.5	5.5	5.3	
Age-adjusted HR (95% CI)	1.0	0.97 (0.93, 1.01)	1.02 (0.98, 1.07)	1.17 (1.06, 1.28)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.00 (0.96, 1.04)	1.02 (0.97, 1.07)	1.07 (0.97, 1.17)	
Model 2	1.0	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)	1.04 (0.94, 1.15)	
Final model	1.0	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)	1.04 (0.94, 1.15)	0.746
Cardiovascular disease-specific					
No. of cases	2,513	1,042	641	117	
Rate per 1,000 person-year	3.3	1.6	1.5	1.4	
Age-adjusted HR (95% CI)	1.0	0.99 (0.92, 1.07)	1.02 (0.93, 1.11)	1.22 (1.02, 1.47)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.01 (0.93, 1.08)	1.00 (0.92, 1.09)	1.08 (0.90, 1.30)	
Model 2	1.0	0.99 (0.92, 1.07)	0.96 (0.88, 1.06)	1.03 (0.84, 1.25)	
Final model	1.0	0.99 (0.92, 1.07)	0.96 (0.88, 1.06)	1.03 (0.84, 1.25)	0.741
Heart disease-specific ǂ	1.0	0.97 (0.88, 1.06)	0.95 (0.85, 1.05)	0.95 (0.75, 1.20)	0.360
Cerebrovascular disease-specific ǂ	1.0	1.07 (0.92, 1.24)	1.01 (0.84, 1.21)	1.26 (0.87, 1.82)	0.361
Cancer-specific					
No. of cases	2,097	1,137	741	152	
Rate per 1,000 person-years	2.8	1.8	1.8	1.8	
Age-adjusted HR (95% CI)	1.0	0.96 (0.89, 1.03)	1.00 (0.92, 1.08)	1.11 (0.94, 1.31)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.00 (0.93, 1.08)	1.01 (0.93, 1.10)	1.05 (0.89, 1.24)	
Model 2	1.0	1.01 (0.93, 1.09)	0.99 (0.91, 1.09)	1.07 (0.90, 1.26)	
Final model	1.0	1.01 (0.93, 1.09)	0.99 (0.91, 1.08)	1.07 (0.90, 1.26)	0.667
Breast cancer-specific ǂ	1.0	0.94 (0.77, 1.16)	1.04 (0.82, 1.30)	0.81 (0.50, 1.31)	0.689
Lung cancer-specific ǂ	1.0	1.12 (0.94, 1.34)	1.04 (0.85, 1.28)	1.09 (0.75, 1.60)	0.677
Colorectal cancer-specific ǂ	1.0	1.00 (0.77, 1.31)	1.05 (0.77, 1.42)	1.29 (0.72, 2.29)	0.421

*Total person-time: 1,897,745 years. †1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Multivariable-adjusted final model.
HR indicates hazard ratio; CI, confidence interval.
Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.
Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.
Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Table 4.3: Mortality Risk* According to Type of Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories

Mortality	Sugar-Sweetened Beverage Consumption†				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-Cause					
			Sweetened bottled water/tea		
No. of cases	10,394	1,759	1,598	392	
Rate per 1,000 person-years	54.8	9.3	8.4	2.1	
Age-adjusted HR (95%CI)	1.0	0.95 (0.91, 1.01)	0.97 (0.92, 1.02)	1.05 (0.95, 1.16)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)	0.98 (0.89, 1.09)	
Model 2	1.0	0.97 (0.92, 1.03)	0.97 (0.91, 1.02)	0.96 (0.87, 1.07)	
Final model	1.0	0.97 (0.92, 1.03)	0.97 (0.91, 1.02)	0.96 (0.87, 1.07)	0.255
			Fruit Drink		
No. of cases	13,296	500	307	40	
Rate per 1,000 person-year	7.8	4.4	4.2	4.5	
Age-adjusted HR (95%CI)	1.0	1.09 (0.99, 1.19)	1.06 (0.95, 1.19)	1.07 (0.78, 1.45)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.10 (1.00, 1.21)	1.07 (0.96, 1.20)	1.00 (0.73, 1.36)	
Model 2	1.0	1.10 (0.99, 1.21)	1.03 (0.92, 1.17)	1.04 (0.74, 1.46)	
Final model	1.0	1.10 (1.00, 1.21)	1.04 (0.92, 1.17)	1.04 (0.74, 1.46)	0.293
			Caloric soft drinks		
No. of cases	10,463	2,002	1,432	246	
Rate per 1,000 person-years	8.4	6.5	5.0	4.0	
Age-adjusted HR (95%CI)	1.0	0.96 (0.91, 1.00)	1.06 (1.00, 1.12)	1.51 (1.33, 1.71)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.98 (0.93, 1.03)	1.04 (0.99, 1.10)	1.35 (1.19, 1.54)	
Model 2	1.0	0.97 (0.92, 1.02)	1.02 (0.96, 1.08)	1.30 (1.14, 1.48)	
Final model	1.0	0.97 (0.92, 1.02)	1.02 (0.96, 1.08)	1.30 (1.14, 1.48)	**0.002**
Cardiovascular disease-specific					
			Sweetened bottled water/tea		
No. of cases	3,341	459	391	122	
Rate per 1,000 person-years	3.1	1.2	1.1	1.4	
Age-adjusted HR (95%CI)	1.0	0.91 (0.83, 1.01)	0.88 (0.80, 0.98)	1.28 (1.06, 1.53)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.93 (0.85, 1.03)	0.89 (0.80, 0.99)	1.16 (0.97, 1.39)	
Model 2	1.0	0.93 (0.84, 1.03)	0.88 (0.78, 0.98)	1.09 (0.90, 1.32)	
Final model	1.0	0.93 (0.84, 1.03)	0.88 (0.78, 0.98)	1.09 (0.90, 1.32)	0.763
			Fruit Drink		
No. of cases	4,082	152	73	6	
Rate per 1,000 person- year	2.4	1.3	1.0	0.7	
Age-adjusted HR (95%CI)	1.0	1.19 (1.01, 1.40)	0.92 (0.73, 1.16)	0.57 (0.26, 1.27)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.19 (1.01, 1.40)	0.93 (0.73, 1.17)	0.55 (0.25, 1.23)	
Model 2	1.0	1.22 (1.02, 1.45)	0.87 (0.68, 1.12)	0.50 (0.19, 1.33)	
Final model	1.0	1.22 (1.02, 1.45)	0.87 (0.68, 1.12)	0.50 (0.19, 1.33)	0.311
			Caloric soft drinks		
No. of cases	3,222	612	428	51	
Rate per 1,000 person-years	2.6	2.0	1.5	0.8	
Age-adjusted HR (95%CI)	1.0	0.98 (0.90, 1.07)	1.13 (1.02, 1.25)	1.38 (1.05, 1.82)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.99 (0.91, 1.08)	1.10 (0.99, 1.22)	1.19 (0.90, 1.57)	
Model 2	1.0	0.97 (0.88, 1.06)	1.05 (0.94, 1.17)	1.13 (0.85, 1.51)	
Final model	1.0	0.97 (0.88, 1.06)	1.05 (0.94, 1.17)	1.13 (0.84, 1.51)	0.247
Cancer-specific					
			Sweetened bottled water/tea		
No. of cases	2,785	640	579	123	
Rate per 1,000 person-years	2.6	1.7	1.7	1.5	
Age-adjusted HR (95%CI)	1.0	1.04 (0.95, 1.13)	1.03 (0.94, 1.12)	0.92 (0.77, 1.10)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	1.05 (0.96, 1.15)	1.03 (0.94, 1.13)	0.88 (0.73, 1.05)	
Model 2	1.0	1.06 (0.96, 1.16)	1.02 (0.93, 1.13)	0.88 (0.73, 1.06)	
Final model	1.0	1.06 (0.96, 1.16)	1.02 (0.93, 1.13)	0.88 (0.73, 1.06)	0.312

Table 4.3: Mortality Risk* According to Type of Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories, Continued

Mortality	Sugar-Sweetened Beverage Consumption†				
	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
Fruit Drink					
No. of cases	3,866	153	93	15	
Rate per 1,000 person-year	2.3	1.3	1.3	1.7	
Age-adjusted HR (95%CI)	1.0	0.93 (0.79, 1.10)	0.92 (0.75, 1.13)	1.16 (0.70, 1.92)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.99 (0.84, 1.17)	0.96 (0.78, 1.18)	1.07 (0.65, 1.78)	
Model 2	1.0	0.97 (0.82, 1.15)	0.91 (0.73, 1.13)	1.21 (0.72, 2.00)	
Final model	1.0	0.97 (0.82, 1.15)	0.91 (0.73, 1.13)	1.21 (0.72, 2.00)	0.826
Caloric soft drinks					
No. of cases	3,004	581	440	102	
Rate per 1,000 person-years	2.4	1.9	1.5	1.7	
Age-adjusted HR (95%CI)	1.0	0.91 (0.83, 1.00)	0.96 (0.86, 1.06)	1.40 (1.15, 1.71)	
Multivariable-adjusted HR (95%CI)					
Model 1	1.0	0.96 (0.88, 1.05)	0.99 (0.89, 1.10)	1.36 (1.11, 1.66)	
Model 2	1.0	0.97 (0.89, 1.07)	0.99 (0.89, 1.10)	1.38 (1.13, 1.69)	
Final model	1.0	0.97 (0.89, 1.07)	0.99 (0.89, 1.10)	1.38 (1.13, 1.69)	**0.029**

*Total person-time: 1,897,745 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea is 8 fluid ounces. Models were reciprocally adjusted for the other beverage types.
HR indicates hazard ratio; CI, confidence interval.
Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.
Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.
Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.1: Age-adjusted Mortality Rates* by Cause of Death in the California Teachers Study Cohort, 1995–2015

Cause of Death	Number of deaths	Age-adjusted mortality rate
Infectious/Parasitic Diseases	341	1.5
Neoplasms	7,726	27.7
Diseases of the blood and blood-forming Organs	89	0.4
Endocrine, nutritional & metabolic diseases	740	3.1
Mental, behavioral, & neurodevelopmental disorders	1,054	5.1
Diseases of the nervous system	2,577	10.9
Diseases of the eye and adnexa	2	0
Diseases of the circulatory system	10,063	49.1
Diseases of respiratory system	2,407	10.6
Diseases of the digestive system	741	3.2
Diseases of the skin and subcutaneous tissues	38	0.2
Diseases of the musculoskeletal system	253	1.1
Diseases of the genitourinary system	491	2.2
Congenital malformations, deformations, and Chromosomal abnormalities	27	0.1
Symptoms, signs and abnormal laboratory findings	135	0.7
External causes of morbidity	619	2.5

* Rate per 10,000 person-years

Supplemental Table 4.2: Age-adjusted Mortality Rates* by Race, Education, and Occupation in the California Teachers Study Cohort, 1995–2015

Characteristic	Number of deaths	Age-adjusted mortality rate
Race		
Asian/Pacific Islander	414	1.4
African-American	820	3.0
Hispanic/Latino	382	1.4
Native American	561	3.2
White	24,535	106.4
Other/Mixed	179	0.7
Unknown	412	2.2
Education †		
Academic/Professional doctorate	276	0.9
Master's degree	2,743	9.4
Bachelor's degree	3,508	12.8
Associate's degree or less	93	0.4
Unknown	20,683	94.7
Occupation ǂ		
Teacher, any kind	4,436	14.0
Pupil services	228	0.7
Administration	249	0.7
Any other combination	147	0.4
Unknown	22,243	102.5
Socioeconomic status		
1st quartile, low	1,303	5.9
2nd quartile, low-medium	4,895	21.8
3rd quartile, medium-high	7,812	33.4
4th quartile, high	10,383	42.6
Unknown	2,910	14.6

*Rate per 10,000 person-years. † Self-reported education was obtained after baseline, during fourth mail-in questionnaire follow-up 2005-2006. Data is limited to the number of participants that completed the questionnaire. ǂ Self-reported occupation was obtained after baseline, during third mail-in questionnaire follow-up 2000-2001. Data is limited to the number of participants that completed the questionnaire. § Socioeconomic status score was developed by combining three 1990 U.S. block census data variables (occupation, education, and family income). Quartile categories were determined ranging from 1 (lowest) to 4 (highest).

Supplemental Table 4.3: Age-adjusted Mortality Rates* by Cause of Death in the California Teachers Study Cohort Participants with Complete Sugar-Sweetened Beverage and Mortality Data, 1995–2015

Cause of Death	Number of deaths	Age-adjusted mortality rate
Infectious/Parasitic Diseases	173	1.2
Neoplasms	4,233	21.7
Diseases of the blood and blood-forming Organs	53	0.3
Endocrine, nutritional & metabolic diseases	275	1.8
Mental, behavioral, & neurodevelopmental disorders	575	4.8
Diseases of the nervous system	1,492	10.1
Diseases of the eye and adnexa	2	0
Diseases of the circulatory system	4,770	39.0
Diseases of respiratory system	1,289	9.2
Diseases of the digestive system	383	2.9
Diseases of the skin and subcutaneous tissues	16	0.3
Diseases of the musculoskeletal system	139	1.0
Diseases of the genitourinary system	244	1.7
Congenital malformations, deformations, and Chromosomal abnormalities	15	0.1
Symptoms, signs and abnormal laboratory findings	67	0.6
External causes of morbidity	417	2.5

*Rate per 10,000 person-years.

Supplemental Table 4.4: Age-adjusted Mortality Rates* by Race, Education, and Occupation in California Teachers Study Cohort Participants with Complete Sugar Sweetened Beverage and Mortality Data, 1995–2015

Characteristic	Number of deaths	Age-adjusted mortality rate
Race		
Asian/Pacific Islander	215	1.0
African-American	422	2.5
Hispanic/Latino	222	1.1
Native American	186	1.8
White	12,868	88.8
Other/Mixed	87	0.5
Unknown	143	1.2
Education		
Academic/Professional doctorate	174	0.9
Master's degree	1,824	9.6
Bachelor's degree	2,287	13.3
Associate's degree or less	49	0.3
Unknown	9,809	72.7
Occupation		
Teacher, any kind	2,855	11.6
Pupil services	141	0.5
Administration	170	0.6
Any other combination	87	0.3
Unknown	10,890	83.8
Socioeconomic status		
1st quartile, low	632	4.7
2nd quartile, low-medium	2,457	17.9
3rd quartile, medium-high	4,115	27.3
4th quartile, high	5,634	36.0
Unknown	1,305	10.7

*Rate per 10,000 person-years. † Self-reported education was obtained after baseline, during fourth mail-in questionnaire follow-up 2005-2006. Data is limited to the number of participants that completed the questionnaire. ǂ Self-reported occupation was obtained after baseline, during third mail-in questionnaire follow-up 2000-2001. Data is limited to the number of participants that completed the questionnaire. § Socioeconomic status score was developed by combining three 1990 U.S. block census data variables (occupation, education, and family income). Quartile categories were determined ranging from 1 (lowest) to 4 (highest).

Supplemental Table 4.5: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*†

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
N	40,579	33,773	21,665	4,297
SSB intake, fl oz/day	0 ± 0.02	2.6 ± 0.02	5.5 ± 0.02	13.6 ± 0.05
Dietary Intake				
Energy, kcal/day	1,756.6 ± 3.36	1,957.5 ± 3.68	2,047.7 ± 4.60	2,248.5 ± 10.32
Carbohydrate, g/day	252.2 ± 0.18	253.9 ± 0.19	260.4 ± 0.24	283.1 ± 0.54
Protein, g/day	80.4 ± 0.07	76.9 ± 0.07	74.5 ± 0.09	68.0 ± 0.20
Total Fat, g/day	59.9 ± 0.07	61.7 ± 0.07	60.0 ± 0.09	53.9 ± 0.20
Fruit & Vegetables, g/day	359.6 ± 0.87	299.9 ± 0.94	285.1 ± 1.18	265.4 ± 2.66
Vegetables, g/day	183.9 ± 0.54	163.4 ± 0.60	163.3 ± 0.74	166.9 ± 1.66
Red meat, g/day	29.1 ± 0.17	34.7 ± 0.19	36.3 ± 0.23	36.8 ± 0.52
Processed meat intake, g/day	6.3 ± 0.06	8.2 ± 0.06	8.4 ± 0.08	8.7 ± 0.18
Age, y	55.3 ± 0.06	48.9 ± 0.07	48.8 ± 0.09	48.6 ± 0.20
Race/ethnicity, %				
Asian/Pacific Islander	1,092 (2.7)	1,518 (4.5)	815 (3.8)	115 (2.7)
African-American	663 (1.6)	1,077 (3.2)	663 (3.1)	117 (2.7)
Hispanic/Latino	1,248 (3.1)	1,720 (5.1)	1,083 (5.0)	180 (4.2)
Native American	296 (0.7)	239 (0.7)	148 (0.7)	25 (0.6)
White	36,568 (90.1)	28,531 (84.5)	18,471 (85.3)	3,774 (87.8)
Other/Mixed	410 (1.0)	447 (1.3)	297 (1.4)	56 (1.3)
Unknown	302 (0.7)	241 (0.7)	188 (0.9)	30 (0.7)
Education, % ǂ				
Academic doctorate	847 (2.1)	590 (1.8)	388 (1.8)	97 (2.3)
Professional doctorate	215 (0.5)	171 (0.5)	127 (0.6)	28 (0.7)
Master's degree	10,640 (26.2)	9,203 (27.3)	5,801 (26.8)	1,182 (27.5)
Bachelor's degree	9,167 (22.6)	7,906 (23.4)	4,612 (21.3)	874 (20.3)
Associate's degree	124 (0.3)	129 (0.4)	95 (0.4)	15 (0.4)
Technical school/certificate/High school	10 (0.02)	8 (0.02)	8 (0.04)	4 (0.09)
Less than High school	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Unknown	19,576 (48.2)	15,765 (46.7)	10,634 (49.1)	2,097 (48.8)
Occupation, %				
Teacher, single grade Pre-K to High school	17,225 (43.6)	18,245 (54.0)	11,919 (55.0)	2,402 (55.9)
Teacher, other	2,972 (7.0)	2,440 (7.2)	1,615 (7.5)	359 (8.4)
Multiple	201 (0.5)	247 (0.7)	141 (0.7)	29 (0.7)
Pupil Services	1,183 (2.8)	1,082 (3.2)	679 (3.1)	132 (3.1)
Administration	1,362 (3.2)	1,195 (3.5)	850 (3.9)	191 (4.4)
Teacher, Pre-K/Elem/Other or JrH/Hi/Other	279 (0.7)	280 (0.8)	180 (0.8)	41 (1.0)
Pupil Services/Administration or Pupil Services/Administration/Teacher combination	416 (1.0)	346 (1.0)	229 (1.1)	42 (1.0)
Unknown	17,512 (41.3)	9,938 (29.4)	6,052 (27.9)	1,101 (25.6)
Socioeconomic status, %				
1st quartile, low	1,422 (3.5)	1,421 (4.2)	914 (4.2)	168 (3.9)
2nd quartile, low-medium	6,124 (15.1)	5,628 (16.7)	3,671 (16.9)	684 (15.9)
3rd quartile, medium-high	12,044 (29.7)	10,736 (31.8)	6,639 (30.6)	1,366 (31.8)
4th quartile, high	17,791 (43.8)	13,905 (41.2)	9,107 (42.0)	1,814 (42.2)
Unknown	3,198 (7.9)	2,083 (6.2)	1,334 (6.2)	265 (6.2)
Marital status, %				
Married	18,668 (46.0)	16,701 (49.5)	10,234 (47.2)	1,995 (46.4)
Divorced	3,540 (8.7)	2,730 (8.1)	1,644 (7.6)	374 (8.7)
Separated	275 (0.7)	287 (0.9)	186 (0.9)	32 (0.7)
Widowed	3,327 (8.2)	1,579 (4.7)	1,011 (4.7)	182 (4.2)
Never married	1,927 (4.8)	1,695 (5.0)	1,100 (5.1)	257 (6.0)
Unknown	12,842 (31.7)	10,781 (31.9)	7,490 (34.6)	1,457 (33.9)
MVPA, minutes/week	240.4 ± 1.23	215.4 ± 1.35	221.7 ± 1.68	222.2 ± 3.78
Smoking, %				
Never	25,642 (63.2)	23,820 (70.5)	14,858 (68.6)	2,799 (65.1)
Former	12,841 (31.6)	8,440 (25.0)	5,658 (26.1)	1,164 (27.1)
Current	2,047 (5.0)	1,487 (4.4)	1,123 (5.2)	329 (7.7)
Unknown	49 (0.1)	26 (0.1)	26 (0.1)	5 (0.1)
Number of cigarettes per day, §	13.2 ± 0.08	11.4 ± 0.10	12.0 ± 0.12	14.4 ± 0.27
Alcohol consumption, g/day, %				
None	13,315 (32.8)	10,633 (31.5)	7,024 (32.4)	1,624 (37.8)
<20	23,219 (57.2)	20,729 (61.4)	13,003 (60.0)	2,347 (54.6)
≥20	4,045 (10.0)	2,411 (7.1)	1,638 (7.6)	326 (7.6)

Supplemental Table 4.5: Comprehensive Baseline Characteristics of California Teachers Study Participants According to Sugar-Sweetened Beverage Consumption Categories*†, Continued

Characteristic	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day
Body mass index, kg/m^2, %				
Underweight (<18.5)	981 (2.4)	903 (2.7)	566 (2.6)	123 (2.9)
Normal (18.5-24.9)	23,062 (56.8)	19,997 (59.2)	12,351 (57.0)	2,258 (52.6)
Overweight (25-29.9)	9,896 (24.4)	7,720 (22.9)	5,109 (23.6)	1,047 (24.4)
Obese (≥30)	5,015 (12.4)	4,145 (12.3)	2,993 (13.8)	752 (17.5)
Unknown	1,625 (4.0)	1,008 (3.0)	646 (3.0)	117 (2.7)
Hypertension, %	7,042 (17.4)	4,134 (12.2)	2,885 (13.3)	616 (14.3)
Aspirin use, %				
Daily	3,268 (8.1)	1,691 (5.0)	1,135 (5.2)	268 (6.2)
Up to 6x/week	5,747 (14.2)	4,881 (14.5)	3,208 (14.8)	689 (16.0)
Regular use, unknown frequency	227 (0.6)	173 (0.5)	135 (0.6)	21 (0.5)
Not regularly taken	30,757 (75.8)	26,611 (78.8)	16,908 (78.0)	3,267 (76.0)
Unknown use	580 (1.4)	417 (1.2)	279 (1.3)	52 (1.2)
Antihypertensive medication, at least 1 medication, use, %				
Daily	6,444 (15.9)	3,562 (10.6)	2,504 (11.6)	547 (12.7)
Up to 6 times per week	539 (1.3)	399 (1.2)	258 (1.2)	76 (1.8)
Regular use, unknown frequency	451 (1.1)	280 (0.8)	198 (0.9)	35 (0.8)
Not regularly taken	32,565 (80.3)	29,117 (86.2)	18,426 (85.1)	3,587 (83.5)
Unknown use	580 (1.4)	415 (1.2)	279 (1.3)	52 (1.2)
Multivitamin use, %				
Daily	16,244 (40.0)	10,777 (31.9)	7,035 (32.5)	1,495 (34.8)
Up to 6 times per week	5,947 (14.7)	6,901 (20.4)	4,067 (18.8)	672 (15.6)
Never	6,436 (15.9)	5,323 (15.8)	3,445 (15.9)	699 (16.3)
Unknown use	11,952 (29.5)	10,772 (31.9)	7,118 (32.9)	1,431 (33.3)
Diabetes family history, % ‖	8,448 (20.8)	6,463 (19.1)	4,213 (19.5)	844 (19.6)
Cardiovascular disease family history, % #	20,804 (51.3)	14,991 (44.4)	9,726 (44.9)	1,970 (45.9)
Cancer family history, % **	22,060 (54.4)	17,511 (51.9)	11,246 (51.9)	2,283 (53.1)
Menopausal status and menopausal HT use, %				
Pre-menopausal	13,120 (32.3)	17,120 (50.7)	10,843 (50.1)	2,129 (49.6)
PP, no HT use	5,474 (13.5)	2,933 (8.7)	1,922 (8.9)	361 (8.4)
PP, past HT use	3,185 (7.9)	1,625 (4.8)	1,080 (5.0)	209 (4.9)
PP, current HT use, Estrogen	6,254 (15.4)	3,633 (10.8)	2,296 (10.6)	477 (11.1)
PP, current HT, Estrogen and Progesterone	7,161 (17.7)	4,428 (13.1)	2,780 (12.8)	520 (12.1)
PP, all other HT combinations	5,385 (13.3)	4,034 (11.9)	2,744 (12.7)	601 (14.0)
Oral contraceptive use, %				
Current	1,549 (3.8)	2,493 (7.4)	1,535 (7.1)	318 (7.4)
Past	23,029 (56.8)	21,556 (63.8)	14,032 (64.8)	2,812 (65.4)
Never	14,466 (35.7)	8,627 (25.5)	5,344 (24.7)	996 (23.2)
Unknown if current or past	1,535 (3.7)	1,097 (3.3)	754 (3.4)	171 (4.0)

*Values are means ± standard error mean or N (percentage). †1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Education was obtained after baseline, during fourth mail-in questionnaire follow-up (2005-2006). **§** Current and former smokers only. ‖ Diabetes family history of first-degree relatives (parent, sibling, offspring). # Cardiovascular disease family history includes heart attack/myocardial infarction and stroke family history of first-degree relatives (parent, sibling, offspring). ****** Cancer family history of first-degree relatives (parent, sibling, offspring). Fl oz indicates fluid ounces; g/day, grams per day; HT, hormone therapy; kcal/day, kilocalories per day; MVPA, moderate-vigorous physical activity; PP, peri- or post-menopausal; SSB, sugar-sweetened beverage; y, years.

Supplemental Table 4.6: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Cups per Day

	Sugar-Sweetened Beverage Consumption					
Mortality	Rare or never	Up to ½ cup	Up to 1 cup	Up to 1 ½ cups	>1 ½ cups	P trend
All Cause						
No. of cases	7,838	4,239	1,078	502	486	
Rate per 1,000 person-years	10.4	5.9	5.2	5.0	4.0	
Age-adjusted HR (95% CI)	1.0	0.95 (0.91, 0.99)	1.07 (1.00, 1.14)	1.16 (1.06, 1.27)	1.27 (1.16, 1.39)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.97 (0.94, 1.01)	1.06 (1.00, 1.13)	1.11 (1.01, 1.22)	1.17 (1.06, 1.28)	
Model 2	1.0	0.96 (0.92, 1.00)	1.04 (0.97, 1.11)	1.06 (0.96, 1.17)	1.15 (1.04, 1.27)	
Final model	1.0	0.96 (0.92, 1.00)	1.04 (0.97, 1.11)	1.06 (0.96, 1.17)	1.15 (1.04, 1.26)	**0.001**
Cardiovascular Disease-specific						
No. of cases	2,513	1,273	291	116	120	
Rate per 1,000 person-years	3.3	1.8	1.4	1.1	1.0	
Age-adjusted HR (95% CI)	1.0	0.98 (0.92, 1.05)	1.06 (0.94, 1.20)	1.03 (0.86, 1.24)	1.29 (1.08, 1.55)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	1.00 (0.93, 1.07)	1.03 (0.91, 1.17)	0.97 (0.80, 1.17)	1.15 (0.96, 1.38)	
Model 2	1.0	0.98 (0.92, 1.06)	0.99 (0.87, 1.13)	0.87(0.71, 1.07)	1.10 (0.91, 1.34)	
Final model	1.0	0.98 (0.91, 1.05)	0.98 (0.86, 1.12)	0.87 (0.71, 1.06)	1.09 (0.90, 1.33)	0.988
Heart disease-specific †	1.0	0.97 (0.89, 1.05)	0.94 (0.80, 1.09)	0.87 (0.68, 1.09)	0.98 (0.78, 1.24)	0.327
Cerebrovascular disease-specific †	1.0	1.02 (0.89, 1.18)	1.15 (0.90, 1.46)	0.90 (0.60, 1.35)	1.47 (1.04, 2.08)	**0.086**
Cancer-specific						
No. of cases	2,097	1,318	361	175	176	
Rate per 1,000 person-years	2.8	1.8	1.7	1.7	1.5	
Age-adjusted HR (95% CI)	1.0	0.94 (0.88, 1.01)	1.04 (0.93, 1.16)	1.12 (0.95, 1.30)	1.12 (0.96, 1.31)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.97(0.91, 1.04)	1.06 (0.95, 1.19)	1.11 (0.95, 1.29)	1.10 (0.94, 1.28)	
Model 2	1.0	0.98 (0.91, 1.05)	1.05 (0.93, 1.18)	1.10 0.94, 1.30)	1.12 (0.95, 1.32)	
Final model	1.0	0.97 (0.91, 1.05)	1.04 (0.93, 1.17)	1.10 (0.93, 1.29)	1.12 (0.95, 1.31)	**0.049**
Breast cancer-specific †	1.0	0.95 (0.78, 1.15)	1.07 (0.79, 1.44)	1.01 (0.67, 1.54)	0.86 (0.56, 1.34)	0.842
Lung cancer-specific †	1.0	1.08 (0.92, 1.28)	1.10 (0.83, 1.44)	1.18 (0.82, 1.70)	1.03 (0.69, 1.54)	0.552
Colorectal cancer-specific †	1.0	1.02 (0.80, 1.31)	0.99 (0.64, 1.52)	1.06 (0.58, 1.93)	1.32 (0.76, 2.28)	0.452

*Total person-time: 1,897,745 years. †Multivariable-adjusted final model. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.

Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.

Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.7: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories after removal of events that occurred at 2 years follow-up (n=100,000)

	Sugar-Sweetened Beverage Consumption †				
Mortality	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-Cause					
No. of cases	7,668	3,489	2,253	419	
Rate per 1,000 person-years	10.2	5.4	5.4	5.1	
Age-adjusted HR (95% CI)	1.0	0.97 (0.93, 1.01)	1.02 (0.98, 1.07)	1.15 (1.04, 1.27)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.99 (0.96, 1.04)	1.02 (0.97, 1.07)	1.05 (0.96, 1.16)	
Model 2	1.0	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)	1.03 (0.93, 1.14)	
Final model	1.0	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)	1.03 (0.93, 1.14)	0.819
Cardiovascular Disease-specific					
No. of cases	2,463	1,020	625	112	
Rate per 1,000 person-years	3.3	1.6	1.5	1.4	
Age-adjusted HR (95% CI)	1.0	0.99 (0.92, 1.07)	1.01 (0.93, 1.11)	1.20 (0.99, 1.45)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.00 (0.93, 1.08)	1.00 (0.92, 1.09)	1.06 (0.88, 1.29)	
Model 2	1.0	0.99 (0.92, 1.07)	0.96 (0.87, 1.05)	1.01 (0.82, 1.23)	
Final model	1.0	0.99 (0.92, 1.07)	0.96 (0.87, 1.05)	1.00 (0.82, 1.23)	0.610
Heart disease-specific ǂ	1.0	0.97 (0.88, 1.06)	0.94 (0.84, 1.05)	0.94 (0.74, 1.20)	0.302
Cerebrovascular disease-specific ǂ	1.0	1.06 (0.92, 1.24)	1.01 (0.84, 1.22)	1.21 (0.82, 1.76)	0.452
Cancer-specific					
No. of cases	2,018	1,098	721	144	
Rate per 1,000 person-years	2.7	1.7	1.7	1.7	
Age-adjusted HR (95% CI)	1.0	0.95 (0.88, 1.03)	1.00 (0.92, 1.09)	1.09 (0.92, 1.29)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.00 (0.92, 1.07)	1.02 (0.93, 1.11)	1.03 (0.87, 1.23)	
Model 2	1.0	1.01 (0.93, 1.09)	1.00 (0.91, 1.10)	1.05 (0.88, 1.25)	
Final model	1.0	1.01 (0.93, 1.09)	1.00 (0.91, 1.10)	1.04 (0.88, 1.24)	0.724
Breast cancer-specific ǂ	1.0	0.94 (0.77, 1.16)	1.04 (0.83, 1.31)	0.81 (0.50, 1.32)	0.703
Lung cancer-specific ǂ	1.0	1.17 (0.98, 1.40)	1.06 (0.86, 1.31)	1.09 (0.74, 1.62)	0.647
Colorectal cancer-specific ǂ	1.0	0.98 (0.74, 1.30)	1.10 (0.81, 1.51)	1.13 (0.61, 2.11)	0.507

*Total person-time: 1,897,362 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Multivariable-adjusted final model. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.

Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.

Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.8: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Cups per Day Frequency Categories after removal of events that occurred at 2 years follow-up (n=100,000)

	Sugar-Sweetened Beverage Consumption					
Mortality	Rare or never	Up to ½ cup	Up to 1 cup	Up to 1 ½ cups	>1 ½ cups	P trend
All Cause						
No. of cases	7,668	4,150	1,062	482	467	
Rate per 1,000 person-years	10.2	5.8	5.1	4.8	3.9	
Age-adjusted HR (95% CI)	1.0	0.95 (0.91, 0.99)	1.08 (1.01, 1.15)	1.14 (1.04, 1.25)	1.25 (1.13, 1.37)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.97 (0.94, 1.01)	1.07 (1.00, 1.14)	1.09 (1.00, 1.20)	1.15 (1.05, 1.26)	
Model 2	1.0	0.96 (0.92, 1.00)	1.05 (0.98, 1.12)	1.04 (0.95, 1.15)	1.13 (1.03, 1.25)	
Final model	1.0	0.96 (0.92, 1.00)	1.05 (0.98, 1.12)	1.04 (0.95, 1.15)	1.13 (1.02, 1.25)	**0.003**
Cardiovascular Disease-specific						
No. of cases	2,463	1,245	287	109	116	
Rate per 1,000 person-years	3.3	1.7	1.4	1.1	1.0	
Age-adjusted HR (95% CI)	1.0	0.98 (0.92, 1.05)	1.07 (0.95, 1.21)	0.99 (0.82, 1.21)	1.28 (1.06, 1.55)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.99 (0.93, 1.07)	1.04 (0.92, 1.18)	0.93 (0.77, 1.13)	1.14 (0.95, 1.38)	
Model 2	1.0	0.98 (0.91, 1.06)	1.00 (0.88, 1.14)	0.83 (0.68, 1.03)	1.09 (0.90, 1.33)	
Final model	1.0	0.98 (0.91, 1.05)	1.00 (0.87, 1.14)	0.83 (0.67, 1.02)	1.08 (0.89, 1.32)	0.887
Heart disease-specific †	1.0	0.97 (0.89, 1.05)	0.95 (0.81, 1.10)	0.84 (0.66, 1.07)	0.97 (0.76, 1.24)	0.292
Cerebrovascular disease-specific †	1.0	1.03 (0.89, 1.18)	1.17 (0.91, 1.49)	0.81 (0.52, 1.24)	1.46 (1.03, 2.08)	0.127
Cancer-specific						
No. of cases	2,018	1,276	354	166	167	
Rate per 1,000 person-years	2.7	1.8	1.7	1.6	1.4	
Age-adjusted HR (95% CI)	1.0	0.94 (0.87, 1.01)	1.05 (0.94, 1.18)	1.09 (0.93, 1.28)	1.09 (0.93, 1.28)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.97 (0.91, 1.05)	1.08 (0.96, 1.21)	1.08 (0.92, 1.27)	1.07 (0.91, 1.26)	
Model 2	1.0	0.98 (0.91, 1.06)	1.07 (0.95, 1.20)	1.08 (0.91, 1.27)	1.10 (0.93, 1.30)	
Final model	1.0	0.98 (0.91, 1.05)	1.06 (0.94, 1.20)	1.07 (0.91, 1.30)	1.09 (0.93, 1.29)	0.089
Breast cancer-specific †	1.0	0.95 (0.78, 1.15)	1.07 (0.79, 1.44)	1.02 (0.67, 1.55)	0.87 (0.56, 1.34)	0.853
Lung cancer-specific †	1.0	1.12 0.95, 1.33)	1.16 (0.88, 1.53)	1.15 (0.79, 1.68)	1.02 (0.67, 1.54)	0.593
Colorectal cancer-specific †	1.0	1.02 (0.79, 1.31)	1.04 (0.67, 1.60)	1.02 (0.55, 1.90)	1.27 (0.72, 2.25)	0.503

*Total person-time: 1,897,362 years. † Multivariable-adjusted final model. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.

Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.

Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.9: Mortality Risk* According to Caloric Soft Drink Consumption in Semi-Quantitative Frequency Categories after removal of events that occurred at 2 years follow-up (n=100,000)

	Caloric Soft Drink Consumption †				
Mortality	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-Cause					
No. of cases	10,241	1,960	1,394	234	
Rate per 1,000 person-years	8.3	6.3	4.9	3.8	
Age-adjusted HR (95% CI)	1.0	0.96 (0.91, 1.00)	1.05 (0.99, 1.11)	1.45 (1.29, 1.67)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.98 (0.93, 1.03)	1.04 (0.98, 1.10)	1.32 (1.16, 1.51)	
Model 2	1.0	0.97 (0.92, 1.02)	1.02 (0.96, 1.08)	1.27 (1.11, 1.45)	
Final model	1.0	0.97 (0.92, 1.02)	1.02 (0.96, 1.08)	1.26 (1.10, 1.45)	**0.008**
Cardiovascular Disease-specific					
No. of cases	3,154	600	415	51	
Rate per 1,000 person-years	2.5	1.9	1.5	0.8	
Age-adjusted HR (95% CI)	1.0	0.98 (0.90, 1.08)	1.12 (1.01, 1.24)	1.43 (1.08, 1.89)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.99 (0.91, 1.08)	1.10 (0.99, 1.22)	1.23 (0.93, 1.63)	
Model 2	1.0	0.97 (0.88, 1.06)	1.05 (0.94, 1.17)	1.17 (0.88, 1.57)	
Final model	1.0	0.97 (0.88, 1.06)	1.05 (0.94, 1.17)	1.17 (0.88, 1.57)	0.201
Cancer-specific					
No. of cases	2,900	561	426	94	
Rate per 1,000 person-years	2.3	1.8	1.5	1.5	
Age-adjusted HR (95% CI)	1.0	0.91 (0.83, 1.00)	0.95 (0.86, 1.05)	1.32 (1.07, 1.62)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.96 (0.87, 1.05)	0.99 (0.89, 1.09)	1.28 (1.04, 1.58)	
Model 2	1.0	0.97 (0.89, 1.07)	0.98 (0.88, 1.10)	1.30 (1.06, 1.61)	
Final model	1.0	0.97 (0.89, 1.07)	0.98 (0.88, 1.10)	1.30 (1.06, 1.61)	0.097

*Total person-time: 1,897,362 years. †1 serving of caloric soft drink is 12 fluid ounces. Models adjusted for other sugar-sweetened beverage types. HR indicates hazard ratio; CI, confidence interval.
Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.
Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.
Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.10: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Semi-Quantitative Frequency Categories after removal of events that occurred at 4 years follow-up (n=99,395)

	Sugar-Sweetened Beverage Consumption †				
Mortality	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-Cause					
No. of cases	7,312	3,350	2,156	406	
Rate per 1,000 person-years	9.7	5.2	5.2	4.9	
Age-adjusted HR (95% CI)	1.0	0.98 (0.94, 1.02)	1.03 (0.98, 1.08)	1.17 (1.06, 1.29)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.00 (0.96, 1.04)	1.02 (0.98, 1.08)	1.08 (0.98, 1.20)	
Model 2	1.0	0.99 (0.95, 1.03)	1.00 (0.95, 1.05)	1.06 (0.95, 1.18)	
Final model	1.0	0.99 (0.94, 1.03)	1.00 (0.95, 1.05)	1.06 (0.95, 1.18)	0.453
Cardiovascular Disease-specific					
No. of cases	2,349	984	596	111	
Rate per 1,000 person-years	3.1	1.5	1.4	1.3	
Age-adjusted HR (95% CI)	1.0	1.01 (0.93, 1.08)	1.01 (0.93, 1.11)	1.26 (1.04, 1.52)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.02 (0.94, 1.10)	1.00 (0.92, 1.10)	1.12 (0.93, 1.36)	
Model 2	1.0	1.01 (0.93, 1.09)	0.96 (0.87, 1.06)	1.06 (0.86, 1.30)	
Final model	1.0	1.00 (0.93, 1.09)	0.96 (0.87, 1.06)	1.06 (0.86, 1.30)	0.924
Heart disease-specific ǂ	1.0	0.98 (0.89, 1.07)	0.94 (0.84, 1.06)	1.00 (0.79, 1.28)	0.535
Cerebrovascular disease-specific ǂ	1.0	1.08 (0.93, 1.26)	1.02 (0.85, 1.23)	1.24 (0.84, 1.83)	0.383
Cancer-specific					
No. of cases	1,863	1,039	682	135	
Rate per 1,000 person-years	2.5	1.6	1.6	1.6	
Age-adjusted HR (95% CI)	1.0	0.97 (0.90, 1.05)	1.02 (0.93, 1.11)	1.09 (0.92, 1.30)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.01 (0.94, 1.09)	1.04 (0.95, 1.13)	1.04 (0.88, 1.25)	
Model 2	1.0	1.02 (0.95, 1.11)	1.02 (0.93, 1.12)	1.08 (0.90, 1.29)	
Final model	1.0	1.02 (0.95, 1.11)	1.02 (0.93, 1.12)	1.08 (0.90, 1.29)	0.406
Breast cancer-specific ǂ	1.0	0.94 (0.76, 1.15)	1.02 (0.81, 1.30)	0.84 (0.52, 1.37)	0.743
Lung cancer-specific ǂ	1.0	1.22 (1.01, 1.47)	1.06 (0.85, 1.32)	1.11 (0.73, 1.68)	0.657
Colorectal cancer-specific ǂ	1.0	1.02 (0.76, 1.36)	1.17 (0.85, 1.61)	1.28 (0.68, 2.39)	0.266

*Total person-time: 1,895,436 years. † 1 serving of caloric soft drink is 12 fluid ounces, 1 serving of sweetened bottled water/tea or fruit drink is 8 fluid ounces. ǂ Multivariable-adjusted final model. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.

Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.

Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.11: Mortality Risk* According to Sugar-Sweetened Beverage Consumption in Cups per Day Frequency Categories after removal of events that occurred at 4 years follow-up (n=99,395)

	Sugar-Sweetened Beverage Consumption					
Mortality	Rare or never	Up to ½ cup	Up to 1 cup	Up to 1 ½ cups	>1 ½ cups	P trend
All Cause						
No. of cases	7,312	3,991	1,012	461	448	
Rate per 1,000 person-years	9.7	5.6	4.9	4.6	3.7	
Age-adjusted HR (95% CI)	100	0.96 (0.92, 0.99)	1.08 (1.01, 1.15)	1.15 (1.04, 1.26)	1.26(1.14, 1.38)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.98 (0.94, 1.02)	1.07 (1.00, 1.15)	1.10 (1.00,1.21)	1.17 (1.06, 1.29)	
Model 2	1.0	0.97 (0.93, 1.01)	1.05 (0.98, 1.13)	1.06 (0.96, 1.17)	1.15 (1.04, 1.27)	
Final model	1.0	0.97 (0.93, 1.01)	1.05 (0.98, 1.13)	1.06 (0.95, 1.17)	1.15 (1.04, 1.27)	**0.002**
Cardiovascular Disease-specific						
No. of cases	2,349	1,200	274	104	113	
Rate per 1,000 person-years	3.1	1.7	1.3	1.0	0.9	
Age-adjusted HR (95% CI)	1.0	0.99 (0.92, 1.06)	1.08 (0.95, 1.22)	1.00 (0.82, 1.22)	1.32 (1.09, 1.60)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	1.01 (0.94, 1.08)	1.05 (0.92, 1.19)	0.94 (0.77, 1.15)	1.19 (0.98, 1.44)	
Model 2	1.0	0.99 (0.92, 1.07)	1.01 (0.89, 1.16)	0.85 (0.68, 1.05)	1.14 (0.93, 1.39)	
Final model	1.0	0.99 (0.92, 1.06)	1.01 (0.88, 1.15)	0.84 (0.68, 1.04)	1.12 (0.92, 1.38)	0.820
Heart disease-specific †	1.0	0.98 (0.89, 1.06)	0.95 (0.81, 1.11)	0.87 (0.68, 1.11)	1.02 (0.80, 1.31)	0.530
Cerebrovascular disease-specific †	1.0	1.04 (0.90, 1.20)	1.20 (0.94, 1.54)	0.78 (0.49, 1.22)	1.47 (1.02, 2.11)	0.125
Cancer-specific						
No. of cases	1,863	1,202	336	158	160	
Rate per 1,000 person-year	2.5	1.7	1.6	1.6	1.3	
Age-adjusted HR (95% CI)	1.0	0.95 (0.88, 1.02)	1.07 (0.95, 1.20)	1.11 (0.94, 1.31)	1.12 (0.95, 1.31)	
Multivariable-adjusted HR (95% CI)						
Model 1	1.0	0.98 (0.91, 1.06)	1.10 (0.98, 1.24)	1.11 (0.94, 1.31)	1.11 (0.94, 1.31)	
Model 2	1.0	1.00 (0.92, 1.07)	1.09 (0.96, 1.23)	1.12 (0.95, 1.33)	1.14 (0.96, 1.36)	
Final model	1.0	0.99 (0.92, 1.07)	1.08 (0.96, 1.22)	1.12 (0.94, 1.32)	1.14 (0.96, 1.35)	**0.026**
Breast cancer-specific †	1.0	0.94 (0.77, 1.14)	1.06 (0.78, 1.44)	1.01 (0.66, 1.55)	0.89 (0.58, 1.38)	0.931
Lung cancer-specific †	1.0	1.15 (0.97, 1.37)	1.19 (0.89, 1.58)	1.20 (0.81, 1.78)	1.01 (0.65, 1.58)	0.530
Colorectal cancer-specific †	1.0	1.05 (0.80, 1.37)	1.11 (0.71, 1.73)	1.15 (0.61, 2.15)	1.43 (0.80, 2.54)	0.231

*Total person-time: 1,897,362 years. † Multivariable-adjusted final model. HR indicates hazard ratio; CI, confidence interval.

Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.

Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.

Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

Supplemental Table 4.12: Mortality Risk* According to Caloric Soft Drink Consumption in Semi-Quantitative Frequency Categories after removal of events that occurred at 4 years follow-up (n=99,395)

	Caloric Soft Drink Consumption †				
Mortality	Rare or never	>rare/never to <1 serving per week	≥1 serving per week to <1 serving per day	≥1 serving per day	P trend
All-Cause					
No. of cases	9,801	1,880	1,320	223	
Rate per 1,000 person-years	7.9	6.1	4.6	3.6	
Age-adjusted HR (95% CI)	1.0	0.96 (0.91, 1.01)	1.04 (0.98, 1.10)	1.47 (1.29, 1.68)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.98 (0.93, 1.03)	1.03 (0.97, 1.13)	1.33 (1.17, 1.52)	
Model 2	1.0	0.97 (0.92, 1.02)	1.01 (0.95, 1.07)	1.27 (1.11, 1.46)	
Final model	1.0	0.96 (0.91, 1.02)	1.02 (0.95, 1.07)	1.27 (1.10, 1.46)	**0.014**
Cardiovascular Disease-specific					
No. of cases	3,018	583	390	49	
Rate per 1,000 person-years	2.4	1.9	1.4	0.8	
Age-adjusted HR (95% CI)	1.0	1.00 (0.91, 1.09)	1.10 (0.99, 1.22)	1.45 (1.10, 1.93)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	1.00 (0.92, 1.10)	1.08 (0.97, 1.20)	1.27 (0.95, 1.69)	
Model 2	1.0	0.99 (0.90, 1.09)	1.04 (0.93, 1.16)	1.20 (0.89, 1.62)	
Final model	1.0	0.99 (0.90, 1.09)	1.04 (0.93, 1.16)	1.20 (0.89, 1.62)	0.227
Cancer-specific					
No. of cases	2,704	528	397	90	
Rate per 1,000 person-years	2.2	1.7	1.4	1.5	
Age-adjusted HR (95% CI)	1.0	0.91 (0.83, 1.00)	0.94 (0.85, 1.05)	1.34 (1.08, 1.66)	
Multivariable-adjusted HR (95% CI)					
Model 1	1.0	0.95 (0.87, 1.05)	0.98 (0.88, 1.09)	1.31 (1.06, 1.62)	
Model 2	1.0	0.97 (0.88, 1.07)	0.98 (0.87, 1.09)	1.33 (1.07, 1.66)	
Final model	1.0	0.97 (0.88, 1.07)	0.98 (0.87, 1.09)	1.33 (1.07, 1.66)	0.091

*Total person-time: 1,897,362 years. † 1 serving of caloric soft drink is 12 fluid ounces. Models adjusted for other sugar-sweetened beverage types. HR indicates hazard ratio; CI, confidence interval.
Model 1 adjusted for: age, race, socioeconomic status, marital status, smoking, alcohol intake, cardiovascular disease family history, cancer family history, diabetes family history, hypertension, physical, aspirin use, multivitamin use, menopausal status, menopausal hormone therapy use, oral contraceptive use, and use of at least one antihypertensive medication.
Model 2 adjusted for: Model 1, body mass index, total energy intake and fruit and vegetable intake.
Final model: All variables in Model 2 with exception of family history of cardiovascular disease, cancer, and diabetes.

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CHAPTER 5:

CONCLUSIONS, PUBLIC HEALTH IMPLICATIONS AND RECOMMENDATIONS

The three previous chapters examined the association between SSB intake and incidence of leading causes of death, CVD and CRC, and risk of mortality. Chapter 2 concluded that daily consumption of at least 1 serving of SSBs was associated with a higher risk of CVD, revascularization, and stroke, in women, after accounting for CVD risk factors, sub-optimal lifestyle behaviors and dietary intake. A higher risk of MI was also observed among women with a daily intake of >1 ½ cups of SSBs. Particularly, daily regular soft drink consumption increased the risk of first CVD event. Chapter 3 determined a non-significant modest association between SSB consumption and CRC risk. This finding was impacted by small number of CRC cases particularly in the highest SSB intake category. Chapter 4 concluded that SSBs were not significantly associated with mortality risk with a conventional exposure categorization scheme. However, daily consumption of >1 ½ cups of SSBs was associated with a higher risk in all-cause and cerebrovascular disease specific-mortality after accounting for cardiometabolic and cancer risk factors, adiposity and dietary intake. Additionally, daily consumption of at least 1 serving of regular soft drink was associated with a higher risk of all-cause and cancer-specific mortality.

These three studies expanded the literature on the unfavorable effects of SSB intake, underscoring the importance of intake reduction and a change in beverage consumption patterns. Bearing in mind the broader context of population health, public health implications of excessive SSB intake are considerably detrimental since these beverages are a frequent, if not the leading, drink of choice for millions across the globe, and a foremost contributor of obesity, T2D, and CVD. Public health implications are particularly concerning for low-income and

middle-income countries where the public health infrastructure is inadequate or threatened by socio-economic and political instability.

Similar to the public health concern on excessive sodium intake, added sugar and SSB intake is well above the recommended levels. In the U.S., regardless of the observed decline in SSBs since the early 2000s, these beverages are still responsible for almost half of all added sugars consumed by Americans aged 2 and older.[1] Thus, a multi-level system-wide approach, versus the long-standing individual level action, should be undertaken in order to effectively subside and if possible, counteract, the negative health effects associated with excessive added sugar and SSB intake. Multi-level strategies that include public health initiatives and campaigns, in partnership with the food industry, that resonate among communities and local networks, and supported by local and federal governmental, are essential to decrease SSB consumption and consequently lower the risk and burden of chronic disease.

As previously mentioned in Chapter 1, worldwide implemented actions have stem from a five-domain strategy and includes: taxation of SSBs, particularly regular soft drinks; limiting access to SSBs in schools and public institutions; specific advertising and marketing restrictions targeting children; food labeling rules and public awareness campaigns; and regulations on government purchasing and subsidies, with additional constraints to procurement of products acquired via government assistant program.[2–6] In addition to these strategies, national system-wide recommendations can include initiatives at the manufacturing, individual, and governmental levels, for effective change. The food industry can innovate flavorful yet unsweetened beverages or drinks with significantly less sugar per serving; as a family and individual, choose water as main source of hydration, create your own carbonated drink with seltzer water and fresh fruit slices, and limit the purchase of SSBs to avoid having these drinks

accessible at home; similar ideas can be implemented at schools and work places, with the addition of enhancing (i.e., adding filters and beautifying) and/or taking ownership of water fountains; at the policy level, the *soda tax* should be implemented and/or encouraged since these beverages only offer empty calories and deemed as *liquid candy*.

Overall, the findings from this dissertation substantiate the existing work on SSBs and further reflect what national guidelines and global recommendations have stipulated in efforts to combat the over-consumption of added sugars, principally SSBs. Although much effort is still required, evidence depicts we are moving in the right direction.

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