1.a. **Full Title:** Substitution of sugar-sweetened beverages for other beverages and the risk of developing coronary heart disease: results from the Harvard Pooling Project of Diet and Coronary Disease

b. **Abbreviated Title (Length 26 characters):** SSB and CHD

2. **Writing Group:**

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AK__ [please confirm with your initials electronically or in writing]

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3. **Timeline:** manuscript is ready for review

4. **Rationale:**

Substitution of water, milk, artificially-sweetened beverage (ASB), plain tea or coffee for SSBs has been associated with a lower risk of weight gain, obesity and T2DM. Results from
intervention studies evaluating the effect of replacing SSBs by other beverages on vascular health showed discrepant results. Results from observational studies suggested that substituting SSBs with fruit juice and water or coffee was associated with a lower risk of metabolic syndrome and stroke, respectively. Little evidence exists on whether substitution of SSB intake by other beverages relates to the risk of developing CHD. We investigated the association between SSB intake and the risk of coronary events and death, and assessed if substitution of coffee, tea, milk, fruit juice and artificially-sweetened beverages (ASB) for SSBs was associated with a reduced risk of coronary events and death.

5. Main Hypothesis/Study Questions:
We aim to assess (1) associations between SSB intake and the risk of incident CHD events and deaths, and (2) if substitution of coffee, tea, milk, fruit juice and artificially-sweetened beverages (ASB) for SSBs was associated with a lower risk of CHD events and deaths.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).
Subjects and Methods
Six of the eleven studies from the Harvard Pooling Project (HPP) of Diet and Coronary Disease were included. The HPP inclusion criteria were prospective studies with ≥150 incident coronary cases, assessment of usual dietary intake, and a validation of the diet assessment method. Only participants aged ≥35 years, without a history of CVD, diabetes, or cancer or extreme energy intake and with information on specific beverage consumption were included. The following studies met these criteria: The Atherosclerosis Risk in Communities Study (ARIC); The Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study (ATBC); The Health Professionals Follow-up Study (HPFS); The Iowa Women’s Health Study (IWHS); The Women’s Health Study (WHS); The Nurses’ Health Study (1980-1986 (NHS 80); 1986-1996 (NHS 86)). Two of the six included studies were randomized primary prevention studies and the others were prospective cohort studies. Adjustment for placebo vs. intervention was performed in the ATBC study, but not in WHS as the trial was ongoing at inclusion into the HPP.

Exposure measures
Diet intake was assessed at baseline by food-frequency questionnaires (FFQ). SSBs included carbonated/non-carbonated and caffeinated/non-caffeinated sodas, sport drinks and fruit drinks with any type of added sugar. Caffeinated coffee included all types of plain coffee with caffeine and total coffee also included decaffeinated coffee. Tea included all types of plain tea. Milk included only non-sweetened cow milk, either whole-fat, low-fat or total milk. Fruit juice included only 100% fruit juice. ASB included any diet drinks sweetened with artificial sweeteners. The volume or frequency of a serving was used to assess the quantity of each beverage consumed daily. Frequency data was converted to volume consumed/day on the basis of the frequency and study-specific serving size for each item. We calculated the consumption of beverage types by summing the related individual beverages listed in each study.

Outcome measures
The outcome measures were fatal CHD and nonfatal MI. Standardized criteria, questionnaires supplemented by medical records, autopsy reports or death certificates reviewed by
physicians25,26, were used to ascertain CHD events and death in each study. In this study, CHD events refer to any first incident CHD events, first event can be fatal CHD, and CHD death refers to total incident CHD death. The IWHS used self-reported CHD events; therefore only CHD death was used. Due to insufficient number of CHD deaths among women in ARIC and WHS, only coronary events were included.

Statistical analyses
Hazard ratios (HRs) with 95% confidence intervals (CIs) for the incidence of coronary events and deaths were calculated by Cox proportional hazards regression. The time metric was survival from entry into the study and stratification on age in months at baseline and calendar year at baseline questionnaire was performed. Person-years of follow-up were calculated from baseline until the date of event, death, or end of follow-up. Follow-up was censored at 10 years to avoid misclassification of exposure. The study-logs (sex-specific in ARIC) of HRs were weighted by the inverse of their variances, and a pooled estimate of the HRs was computed using the fixed-effects model, analyses using the random-effects model were also run as sensitivity analyses (Supplementary data). Between-study heterogeneity was calculated using the I-squared (I2) test. Effect modification by sex was also investigated by the I2 test for between-group heterogeneity.

SSB was primarily modelled continuously. Categorical analyses (<1 serving/d; 1-2 serving/d; >2 servings/d) were also performed (Supplementary data). The effect of substituting another beverage for SSBs was calculated by including them in the same model and taking the difference in the individual effect estimates (β-coefficients). The 95% CI for the substitution effects were calculated using variances and covariance of the effect estimates for each beverage. Women and men have different risk of CVD27, therefore, sex-specific associations were also calculated.

Potential confounders and mediators were considered and stepwise added into the analyses. Nutrient intake, including quintiles of cereal-fiber; trans-fat; poly-unsaturated fat: saturated fat ratio, was included in the model as potential confounders. TEI and BMI were considered both confounders and mediators; therefore they were added to the model individually. Baseline hypertension and high cholesterol were also added to the model as potential confounders. The crude model included only SSB and the stratification variables (smoking, physical activity, education, alcohol intake); model 1 further considered confounding by nutrients intake; model 2 further included total energy; model 3 further included BMI; and model 4 further included baseline hypertension and high cholesterol.

Individuals developing CHD in the first years of follow-up may have changed their dietary consumption due to pre-existing symptoms. Therefore, sensitivity analyses excluding individuals who developed CHD within the first two years of follow-up were performed.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes _____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _____ Yes __X__ No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes  _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  _X___ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* __________)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at  http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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