1.a. Full Title:
The Association of Diet Beverage intake with Micro and Macrovascular Outcomes in Persons with Diabetes

b. Abbreviated Title (Length 26 characters):
Diet Beverages and Outcomes

2. Writing Group:
Writing group members:
Lyn Steffen

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

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3. Timeline:
4. **Rationale:**

There is an increasingly strong public and public health interest in the role NNS and diet beverages may play in health.\(^1\) Consumption of NNS has steadily increased over the last 30 years and beverages sweetened with NNS are the largest single contributor to overall NNS intake.\(^2,3\) Intake of these beverages steadily increases with age,\(^1,2,4\) and is much greater in people with diabetes than those without the disease.\(^5,6\) This “mismatch” between sweetness and actual calories in diet beverages has raised interest and concern in how they may relate to health. Especially since these beverages are marketed as a healthy beverage suitable for weight loss and thus diabetes prevention and control; and the population consuming them tend to be looking to lose weight.\(^3,7,8\) The characteristics of diet beverages along with consumption trends, potential linked health issues, and lack of study have been raised in prominent forums as a public health issue.\(^1,9,10\) There are no published studies that have examined the association between diet beverage intake and macrovascular and microvascular outcomes in persons with diabetes.

5. **Main Hypothesis/Study Questions:**

The main objective of this study is to examine the association of diet beverage intake in persons with diabetes (~1,890) at enrollment in the study and incidence of CVD, and microvascular outcomes (diabetic retinopathy / diabetic neuropathy / diabetic nephropathy as available). The analysis will examine diet beverage intake in the framework of the overall dietary pattern. The main hypothesis is that a higher level of diet beverage intake will positively associate with CVD/microvascular outcomes relative to no diet beverage intake.

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).**

This will be a prospective analysis including all participants at baseline with diabetes and have the following data: demographic measures, clinical factors, medication use, dietary intake and other health behaviors. The main outcome of interest will be incident CVD (MI, resuscitated cardiac arrest, definite angina, probable angina (revascularization), stroke, stroke death, chd death, other atherosclerotic death, other CVD death). Within the overall CVD incidence sensitivity analyses will also examine hard CVD, hard CHD, and all CHD outcomes. Secondary outcomes of interest (as available) are microvascular outcomes (diabetic retinopathy / diabetic neuropathy / diabetic nephropathy). Per the
overview of the study, and published papers, it is noted that these microvascular outcomes may be limited to one time point or not available (neuropathy).

In addition to the individual analysis of ARIC data on this topic, ARIC data will also be pooled with data from other studies that also have a comprehensive set of commonly measured variables and longitudinal follow-up for events, specifically MESA, Cardiovascular Health Study, Jackson Heart Study and the Framingham Offspring Study. Careful attention will be paid to the potential overlap of some Jackson Heart study and ARIC participants so they are not doubly included in the pooled data.

We will use Cox proportional hazards models to examine the association between diet beverage intake and CVD with adjustment for demographic, lifestyle, clinical factors (e.g. lipids, BP) and medication use. We will do this in the context of the overall dietary pattern, which we will derive using principal components analysis as well as with an a priori approach using previous approaches \(^{11,12}\), as the overall diet pattern separate from diet beverage intake will be a covariate. We will consider important potential effect modifiers of the association in age, sex, race, smoking, as well as diabetes characteristics (e.g. duration). Further sensitivity analyses accounting for follow up time will also be carried out. In the pooled analysis we will account for different dietary assessments, protocols and assays so the data are harmonized.

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

Possibly- depending on availability of relevant microvascular outcomes (diabetic retinopathy / diabetic neuropathy / diabetic nephropathy) in the study for analysis.

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? __x__

   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)?

Nothing closely related to this proposal

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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Bibliography & References Cited

2. Popkin BM. Patterns of beverage use across the lifecycle. Physiol Behav. 2010;100(1):4-9.