ARIC Manuscript Proposal # 1364

PC Reviewed: 5/13/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Sweetened beverage consumption and development of chronic kidney disease, hyperuricemia, and albuminuria.

b. Abbreviated Title (Length 26 characters): Sweetened Beverages and CKD

2. Writing Group:

Abhijit V. Kshirsagar	Lyn M. Steffen
Vimal Derebail	David A. Shoham
Andrew S. Bomback	Gerardo Heiss

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AVK

F**irst author**: **Abhijit V. Kshirsagar**
Address: UNC Kidney Center
7017 Burnett-Womack Hall
CB# 7155
Chapel Hill, NC 27599-7155

Phone: (919) 966-2561 Fax: (919) 966-4251
E-mail: abhijit_kshirsagar@med.unc.edu

Corresponding/senior author (must be an ARIC investigator for the proposal but can be different in the published paper; correspondence will be sent to both the first author & the corresponding author**)**: Gerardo Heiss
Address: Bank of America, Suite 306
CB # 8050
Chapel Hill, NC 27599-8050

Phone: (919) 962-3253 Fax: (919) 966-9800
E-mail: Gerardo_Heiss@unc.edu

3. Timeline:

Obtain Data Set:	May 2008
Begin Data Analysis:	June 2008
Complete Data Analysis:	October 2008
Manuscript Preparation:	December 2008

4. Rationale:

High fructose corn syrup (HFCS) was introduced in 1967 as an inexpensive but potent sweetener of soft drinks and fruit beverages. Consumption of HFCS has increased nearly 2000%[1] over the past decades and has paralleled the epidemics of obesity, metabolic syndrome, and chronic kidney disease. Estimates from the US Department of Agriculture report the yearly intake of high-fructose corn syrup (HFCS) as an added sweetener to be as high as 62.4 pounds per person. Sweetened beverages account for 72% of this intake.[2]

Analysis of data from the Health Professionals Follow-up Study and the Nurses' Health Studies identified fructose to be independently associated with the development of kidney stones.[3] The Health Professionals Follow-up Study also demonstrated an increase in the incidence of gout among those with high levels of fructose intake.[4] Finally, fructose consumption in NHANES III was found to be associated with an increase in serum uric acid levels.[5] These latter two associations are particularly relevant in regards to chronic kidney disease.

The metabolism of fructose is unique to that of other sugars in that it leads to depletion of hepatic ATP, increasing the degradation of nucleotides and driving the synthesis of uric acid.[6] In animal models, this hyperuricemia produced by high fructose consumption produces a metabolic syndrome and is associated with glomerular hypertension, renal hypertrophy, renal cortical vasocontriction, and arteriolopathy of renal vasculature.[6,7] Decreasing uric acid production with allopurinol attenuates this same metabolic syndrome. In other animal models, high fructose feeding is associated with elevation of substances associated with oxidative stress in the kidney.[8] Models of chronic kidney disease also demonstrate reductions in creatinine clearance and increases in proteinuria in high-fructose fed animals.[9]

The present epidemiologic data and biological models suggest that consumption of large amounts of fructose, particularly in the form of HFCS, not only leads to the development of metabolic syndrome, obesity and hyperuricemia, but may also lead to kidney disease. Evaluation of data from NHANES also suggest that such an association may exist.[10] However, to date, there has been no published investigation of the association between sweetened beverage consumption, kidney disease, and albuminuria.

5. Main Hypothesis/Study Questions:

The consumption of large quantities of sweet beverages, primarily sweetened with high-fructose corn syrup (HFCS), is associated with incident CKD and with albuminuria.

A secondary hypothesis is that consumption of large quantities of sweetened beverages is associated with hyperuricemia.

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).

Study Design:

Phase 1: Cross-sectional analysis.
The first portion of the study will use data from visit 1 to determine whether consumption of sweetened drinks is associated with chronic kidney disease and hyperuricemia.

Outcome: The primary outcome variable of interest (dependent variable) will be presence (or absence) of chronic kidney disease, defined by estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m^2.
eGFR will be calculated by the following formula:

eGFR = 186 * (Serum creatinine)$^{-1.154}$ * (age)$^{-0.203}$ * 1.212(if black) * 0.742(if female

The secondary outcome will be hyperuricemia as defined by uric acid ≥ 7.0mg/dl for men and ≥ 5.7 mg/dl for women.

Exposure: The primary exposure (independent variable) will be dietary intake of sugar-sweetened beverages (regular soft drinks and fruit flavored punch). At visit 1, dietary intake of beverages is divided into coffee, tea, low calorie soft drinks, regular soft drinks, and fruit flavored non-carbonated beverages. The response categories range from > 6 per day to almost never (a total of nine gradations).
Sugar-sweetened beverages will be defined as regular soft drinks and fruit flavored non-carbonated beverages. The exposure variable will be divided into tertiles of consumption.

Inclusion/Exclusion: All participants with available data regarding dietary intake of beverages will be included in the analysis. Those without these data will be excluded.

Phase 2: Prospective analysis
The second portion of the study will pertain to data obtained from visits 2 and 4. Patients will be followed prospectively from the baseline visit (visit 1) through visit 4 to determine if consumption of high fructose corn syrup in the form of sugar-sweetened beverages is associated with the development of incident chronic kidney disease (CKD).

Outcome: The primary outcome variable will be eGFR, estimated by serum creatinine measured at visits 2 and 4. The secondary outcome variable will be presence of albuminuria as defined by albumin to creatinine ratio with sex-specific cutpoints of ≥ 17mg/g in males and ≥ 25mg/g in females. This variable is measured only at visit 4. Hyperuricemia (defined above with sex-specific cutpoints of ≥ 7.0 mg/dl and ≥ 5.7 mg/dl for men and women, respectively) will also be a secondary outcome in this phase using uric acid levels measured at visit 2.

Exposure: Dietary intake of sugar-sweetened beverages, measured at visit 1 will be the primary exposure with the same categories as defined in Phase 1.

Inclusion/Exclusion: Patients without dietary beverage intake data will be excluded. For the prospective analysis, patients with eGFR <60ml/min/1.73m^2 at visit 1 will be excluded from the analysis.

Data Analysis:

1. For Phase 1, logistic regression models will be used to determine odds ratios for the association of sugar-sweetened beverage intake and prevalent CKD (eGFR < 60 ml/min/1.73 m^2). Logistic regression models will also be used to determine the association of sugar sweetened beverage intake with hyperuricemia, as defined previously.

2. For Phase 2, three main analyses are planned.
The first is a logistic regression model to determine the association of sugar-sweetened beverage intake (from visits 1) with incident CKD (eGFR < 60 ml/min/1.73 m^2). Measures of incident CKD will be available at visit 2 and 4. The second analysis will determine association of sugar-sweetened beverage intake with incident hyperuricemia (from visit 2). The third analysis is to determine the association of sugar sweetened beverage intake with (new) albuminuria measured at visit 4.

3. In both phases, we will investigate for the presence of effect modification by hyperuricemia of the relationship of sugar-sweetened beverage intake with CKD. Presence or absence of hyperuricemia as defined by the above noted sex-specific cutpoints will be determined from visit 1.

4. For both phases, multivariable models will be constructed to adjust for necessary covariables including age, race, sex, body mass index (BMI), smoking, diabetes mellitus, hypertension, education level, salt intake, and ARIC field center.

Limitations:

The major limitation to this study is the reliance on self-reporting of dietary intake measures. The major limitation to this study is the reliance on self-reporting of dietary intake measures. In addition, the Willett 66-item food frequency questionnaire is known to underestimate energy intake due to the limited number of food categories. However, in this case, everyone's usual energy intake will be underestimated. Dietary intake may also be misclassified by this questionnaire, contributing to measurement error in the point estimates that may potentially result in large biases either towards or away from the null.[11] We will explore the effects of bias due to measurement error and will consider correction for that error.[12,13]

7.a. Will the data be used for non-CVD analysis in this manuscript? _X__ Yes ____ 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? __X_ Yes ____ No
(This file ICTDER03 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)?
Proposal # 1209r, Foods, Dietary Patterns & Microalbuminuria
Lead Author: Nettleton, J.
Propoal # 1344, Correlates of Gout and Its Association with Kidney Function: the Atherosclerosis Risk in Communities Study
Lead Author: Kottgen, A.

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/

12. 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.

References:

1. Gross LS, Li L, Fore ES, et al. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr 2004; 79:774-779

2. Putnam JJ, Allshouse JE. *Food Consumption, Prices and Expenditures, 1970–1997.* Washington, DC: Economic Research Service, US Dept of Agriculture; 1999.

3. Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. Kidney International 2008; 73: 207-212.

4. Choi HK, Curhan GC. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. British Medical Journal 2008; 336: 309-312.

5. Choi JWJ, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the third national health and national nutrition examination survey. Arthritis and Rheumatism 2008; 59: 109-116.

6. Nakagawa T, Hu H, Zharikov S et al. A causal role for uric acid in fructose-induced metabolic syndrome. American Journal of Physiology, Renal Physiology 2006; 290: 625-631.

7. Sanchez-Lozada LG, Tapia E, Jimenez A et al. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. American Journal of Physiology, Renal Physiology 2007; 292: F423-F429.

8. Bell RC, Carlson JC, Storr KC, Herbert K, Sivak J. High-fructose feeding of streptozotocin-diabetic rats is associated with increased cataract formation and increased oxidative stress in the kidney. British Journal of Nutrition 2000; 84: 575-582.

9. Gersch MS, Mu W, Cirillo P et al. Fructose, but not dextrose, accelerates the progression of chronic kidney disease. American Journal of Physiology, Renal Physiology 2007; 293: F1256-F1261.

10. Shoham DA, Vupputuri S, Kshirsagar AV. Soft drink consumption and albuminuria: NHANES 1999-2004. Poster Presentation at 40th Annual Meeting of the American Society of Nephrology. J Am Soc Nephrol 18, 2007.

11. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, Bingham S, Schoeller DA, Schatzkin A, Carroll RJ. Structure of dietary measurement error: results of the OPEN biomarker study. Am J Epidemiol. 2003; 158: 14-21.

12. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T, Folsom AR. Reliability of a food frequency questionnaire by race, gender, age and education. Nutr Res. 1996; 16: 735-45.

13. Beaton GH, Milner J, Corey P, McGuire V, Cousins M, Stewart E, de Ramos M, Hewitt D, Grambsch PV, Kassim N, Little JA. Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. *Am J Clin Nutr*. 1979; 32: 2546-59.