ARIC Manuscript Proposal # 3173

PC Reviewed: 07/10/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of dietary choline and betaine with the risk of type 2 diabetes

b. Abbreviated Title (Length 26 characters): **Choline, betaine and type 2 diabetes**

2. Writing Group:
Writing group members: Daniel T. Dibaba, PhD, MPH; Justin Xavier Moore, PhD, MPH; Aurelian Bidulescu, PhD, MD; Steven H Zeisel, PhD, MD

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

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3. Timeline: May 15-June 30: Get data
July 1-Sept 30, 2018: Data preparation and Analysis
October 1-December 31, 2018: Prepare Manuscript
January 1-March 30, 2019: Distribute Manuscript to co-authors for critical review and approval and then submit to ARIC before publication.

4. Rationale:

Observational studies indicate dietary phosphatidylcholine is directly associated with the risk of type 2 diabetes (1). Furthermore, in animal studies choline supplementation increased insulin resistance in phosphatidylcholine N-methyl transferase deficient mice via increased action of glucagon (2). In another animal study, choline deficiency attenuated body weight gain and improved glucose tolerance in mice models (3). In humans, systemic and urinary metabolites of choline, betaine was significantly associated with incident type 2 diabetes, plasma betaine being inversely associated while urinary betaine was directly associated (4). Similarly, trimethylamine-N-oxide (TMAO) a microbiota-dependent metabolite of dietary choline is directly associated with the risk of type 2 diabetes in a case control study (5). Choline is converted to betaine, which is in turn metabolized to form the universal methyl donor-S-adenosylmethionine (SAM). Both choline and betaine transport lipids from liver and are linked to insulin resistance(6). Given that SAM is a one-carbon donor, it may have epigenetic impacts on the risk of type 2 diabetes. The focus of most of the previous studies has been on the association of choline metabolites with the risk of type 2 diabetes. However, data on whether dietary intake of choline and/or betaine predict the risk of type 2 diabetes is sparse.

Type 2 diabetes is a major health problem globally and the prevalence is highest among Blacks in the USA (7). The major risk factors of type 2 diabetes include obesity, physical inactivity, age, and family history of diabetes, fat distribution, diet, and alcohol (8, 9). Obesity is also highly prevalent among Blacks (10, 11) and may be one of the driving factors for the high prevalence of type 2 diabetes in this population. To the best of our knowledge, whether dietary choline and betaine are associated with risk of type 2 diabetes among Blacks is not widely investigated.
In the proposed study, we aim to investigate the longitudinal association of dietary choline and betaine with the risk of type 2 diabetes in the Jackson Heart Study.

5. Main Hypothesis/Study Questions:
Hypothesis 1: Dietary choline is directly associated with increased risk of type 2 diabetes.
Hypothesis 2: Dietary betaine is inversely associated with the risk of type 2 diabetes.

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).

We will compared baseline characteristics of participants by type 2 diabetes status using chi-squared test or Kruskal-Wallis test as appropriate. We will examine the association between continuous exposures (choline and betaine) as well as their quantiles with the risk of type 2 diabetes adjusting for potential confounding variables using Cox proportional hazard regression models or logistic regression in case there is wide interval censoring or if time to event is not available. We will conduct sensitivity analysis to investigate potential differences in the association by sex.

Data:
Exposure: baseline dietary choline, dietary betaine
Outcome: time to type 2 diabetes, type 2 diabetes diagnosis date, fasting blood glucose, HgA1C

Type 2 diabetes is defined as present if at least one of the following criteria is met. The criteria are:
1) Fasting blood glucose level of ≥126 mg/dL
2) Non-fasting blood glucose ≥200 mg/dL
3) Using medication for diabetes 4) Self-reported diagnosis of diabetes 5) Hemoglobin value ≥6.5%.

Covariates: HOMA-IR, family history of diabetes, baseline and incident type 2 diabetes status and diabetes medication, age, sex, body mass index (weight, height) ,alcohol, smoking, income, education, physical activity, dietary variables such as calorie intake, fiber, vitamins, minerals, and fatty acids, glycemic index, coffee; HDL, LDL, triglyceride, systolic blood pressure, diastolic blood pressure, participant id, menopausal status (for females)

Inclusions/Exclusions:
Participants will be excluded from the proposed analysis if they have baseline type 2 diabetes, gestational diabetes, insulin resistance, glucose intolerance, and cardiovascular disease; if they have substantial missing values in dietary choline, dietary betaine, type 2 diabetes, or other relevant covariates. All participants with complete data on exposure variables, covariates and outcome variables will be considered for inclusion the study.

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 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.

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.

References

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