ARIC Manuscript Proposal #2844

PC Reviewed: 09/13/16   Status: ____   Priority: 2
SC Reviewed: _____   Status: ____   Priority: ___

1.a. Full Title: The influence of caloric intake and dietary composition on mortality, congestive heart failure and cardiac structure and function in the community

b. Abbreviated Title (Length 26 characters): Dietary composition, death, HF and echo

2. Writing Group:
Writing group members: Sara B. Seidelmann, Brian Claggett, Amil Shah, [OTHERS WELCOME], Scott D. Solomon

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3.   Timeline: Analysis will begin following proposal approval with the aim of completing the analysis and associated manuscript(s) within 1 year of data availability.

4.   Rationale:

The relationship between dietary intake and lifespan has been postulated since the age of Hippocrates. In the modern era, the study of diet and lifespan began almost 100 years ago, in 1917, when Osborne and colleagues reported a small study showing that reducing the dietary caloric intake of lab rats led to an increase in lifespan. Since this time, the reduction of food intake, termed "caloric restriction" (access to food is reduced by 10%-50% of ad libitum intake), has emerged as an established model to study aging. The study of caloric restriction in animal models has led to the understanding of nutrient-sensing pathways that connect diet and aging, including the sirtuin (SIRT), mechanistic target of rapamycin (mTOR), 5' adenosine monophosphate-activated protein kinase (AMPK), and insulin/insulin-like growth factor-1 (IGF-1)/Growth Hormone pathways[1]. Genetic and pharmacological interventions of nutrient-sensing pathways have been shown to delay or accelerate aging in animal models[2]. However, it has been debated whether the lifespan benefit of caloric restriction is secondary to a reduction in calories or a reduction/increase in one of the macronutrient components (protein, fat or carbohydrate). Scientists have used a methodological approach, called the Geometric Framework, to attempt to answer this question in animal models. Using this approach, evidence from insects through higher vertebrates has suggested that ad libitum-fed diets that are lower in protein and higher in carbohydrate (LPHC) are associated with longer lifespan, while moderately reduced total calorie intake has no effect or is slightly detrimental (reviewed in [3]).

Congestive heart failure (HF) can be thought of as a disease of aging. In fact, it is the most common reason for hospitalization in individuals over the age of 65 in the US. It carries a poor prognosis with 5-year mortality rates similar to many cancers. Based on the Framingham Heart Study, after a new diagnosis of HF, 30-day mortality is approximately 10%, 1-year mortality is 20%-30%, and 5-year mortality is 45%-60%[4]. Several observational studies have assessed the relationship of low carbohydrate high protein diets on all-cause or CV mortality[5-9]. However, studies assessing incident heart failure, particularly with cardiac structure and function, are lacking. We hypothesize that variation in dietary composition may play a role in incident heart failure and mortality. Further, we hypothesize that dietary composition will predict changes in cardiac structure and function.

5.   Main Hypothesis/Study Questions:

1. We hypothesize that total caloric intake may have a relatively small association with mortality, heart failure as well as cardiac structure and function.
2. We hypothesize that dietary composition (percent of total calories derived from carbohydrate, protein or fat), adjusted for total caloric intake, may have

a significant association with mortality, heart failure as well as cardiac structure and function.

3. We hypothesize that total caloric intake and dietary composition will be deferentially associated with all-cause mortality and heart failure versus atherosclerotic etiologies of cardiovascular disease.

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).

Exposures:
Nutrition data from Visit 1 and Visit 3 will be utilized. Dietary composition (percentage of total kcal from fat (total, animal, vegetable, saturated and unsaturated), protein (animal and vegetable), carbohydrate, food and food group serving/day, as well as micronutrient data will be assessed.

Specifically, we will examine:
1) total calories
2) percent of total kcal that are carbohydrates (expressed in quintiles)
3) percent of total kcal that are protein (expressed in quintiles)
4) percent of total kcal that are fat--percent animal fat, percent vegetable fat (expressed in quintiles)
5) composite score of low carb high protein (expressed in quintiles) +/-high fat

Outcomes:
Primary Outcomes--The outcomes studied will be death and cardiovascular events since the first visit. We will evaluate all cause mortality, stroke (fatal or non-fatal), CHD (fatal or non-fatal MI or CHD death), HF (including both systolic heart failure and heart failure with preserved ejection fraction) since the first visit to the latest adjudication (currently 2013) among subjects who were free of these outcomes at the beginning of visit one. HF treatment prior to event (ACEi, ARB, beta blocker, MRA, digoxin, statins, diuretics) will also be evaluated.

Secondary Outcomes— Cardiac structure and function at Visit 5 by echocardiography including measures of ventricular volumes, atrial volumes, systolic function (ejection fraction and strain), Doppler measures of diastolic function. Blood Pressure - systolic and diastolic blood pressure measured at visits 1-5 and hypertension status will be evaluated. Diabetic and metabolic related phenotypes-- Total cholesterol, high density lipoprotein, diabetes mellitus status, HbA1C, body weight, BMI, waist-to-hip ratio, percent body fat, fat mass, lean body mass, fasting glucose, insulin levels will be assessed. Oral glucose tolerance test results will also be assessed.

Confounders:

Age, gender, race, education, income level, physical activity, marital status, married couples in ARIC will be utilized to evaluate confounding for socioeconomic factors, diabetes mellitus status, HbA1C, body weight, BMI, waist-to-hip ratio, cholesterol levels, blood pressure, caloric consumption at baseline.

Analysis plan:

Descriptive statistics: Descriptive statistics of the study sample will be presented by quantiles of total caloric intake as well as by quantiles of dietary composition. Further, scores for LCHP (+/- quantiles of animal fat) will be generated by adding quantile rank (or reverse quantile rank) scores. Categorical data will be displayed as percent frequencies and compared by $\chi 2$ or Fisher exact tests. Continuous data will be displayed as means (±SD) for normally distributed variables and medians (interquartile range) for variables with skewed distributions and compared between groups via Wilcoxon rank sum test or nonparametric trend tests as appropriate. We will utilize univariable and multivariable linear regression models for the analysis to examine the cross-sectional associations of each dietary component and quantitative characteristics. Basic, age- and gender-adjusted, as well as covariate adjusted hazard ratios will be used to test the association between dietary factors and the risk of death, cardiovascular outcomes and heart failure using Cox proportional hazards regression.

Limitations: understandably there will be a significant degree of intra-individual variability in dietary measures.
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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)?**

Past (inactive) proposals:

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ___ Yes __x__ No.

References:

1. Solon-Biet, S.M., et al., *Macronutrients and caloric intake in health and longevity.* J Endocrinol, 2015. **226**(1): p. R17-28.
2. Le Couteur, D.G., et al., *Aging biology and novel targets for drug discovery.* J Gerontol A Biol Sci Med Sci, 2012. **67**(2): p. 168-74.
3. Le Couteur, D.G., et al., *The impact of low-protein high-carbohydrate diets on aging and lifespan.* Cell Mol Life Sci, 2016. **73**(6): p. 1237-52.
4. Bui, A.L., T.B. Horwich, and G.C. Fonarow, *Epidemiology and risk profile of heart failure.* Nat Rev Cardiol, 2011. **8**(1): p. 30-41.
5. Fung, T.T., et al., *Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies.* Ann Intern Med, 2010. **153**(5): p. 289-98.
6. Lagiou, P., et al., *Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study.* BMJ, 2012. **344**: p. e4026.
7. Lagiou, P., et al., *Low carbohydrate-high protein diet and mortality in a cohort of Swedish women.* J Intern Med, 2007. **261**(4): p. 366-74.
8. Sjogren, P., et al., *Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden.* Am J Clin Nutr, 2010. **92**(4): p. 967-74.
9. Trichopoulou, A., et al., *Low-carbohydrate-high-protein diet and long-term survival in a general population cohort.* Eur J Clin Nutr, 2007. **61**(5): p. 575-81.