ARIC Manuscript Proposal # 1182

PC Reviewed: _08__/_15__/06 **Status: __A___** **Priority: __2__**
SC Reviewed: _08__/_17__/06 Status: __A__ Priority: __2__

1.a. Full Title:
Diet and the risk of congestive heart failure in the Atherosclerosis Risk in Communities Study (ARIC)

1.b. Abbreviated Title:
Diet and congestive heart failure

2. Writing Group:
Writing group members: Jennifer A. Nettleton, Lyn M. Steffen, Lloyd E. Chambless, Wayne D. Rosamond, Aaron R. Folsom (other interested investigators welcome)

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

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3. Timeline:

Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized.
Initial drafts will be circulated among the writing group members within four months of proposal approval.

4. Background & Rationale:

There is a growing body of evidence to support the notion that congestive heart failure (CHF), like other cardiovascular diseases, may be importantly related to dietary factors (1-4). Given the shared antecedents of these diseases as a whole (high blood pressure, obesity, diabetes/insulin resistance, coronary heart disease), the relation between diet and CHF is not surprising. However, relative to other cardiovascular diseases, the role of diet in the development of CHF is, to date, understudied.

The value of sodium restriction in patients with CHF is fairly undisputed and is a general recommendations for dietary management in CHF (3-5) along with standard pharmacological treatment, including diuretics which may further contribute to marginal nutritional status. For example, loop diuretics may increase secretion of calcium and thiamin (6). Placebo controlled trials have shown that supplementation of these and other micronutrients, singly (7-11) or as a cocktail (6, 12), can improve functional status and associated quality of life measures. However, the degree of efficacy reported in these trials has varied with some reporting no effects (13-15), possibly owing, in part, to inadequate study design or insufficient participant

numbers (16, 17). Further, most of these investigations have largely ignored the potential for synergistic effects of the nutrients when consumed within the food matrix (1). It is widely recognized the effects of nutrient supplementation may not mimic the effects of consuming the same nutrients from foods (18, 19). The DASH trials demonstrating efficacious reduction in blood pressure are excellent examples of the value of foods and dietary pattern (20-23). Furthermore, the results of these trials suggest similar potential for prevention of CHF since hypertension is a major risk factor for CHF.

Although current knowledge precludes definitively concluding micronutrient deficiencies, such as those observed in persons with CHF (e.g., thiamine, magnesium, calcium, folate, selenium), are precursors to, rather than results of disease, studies suggest that symptom management and improvement in overall quality of life significantly improve following nutritional intervention (24). Critical investigation of the temporal relation between diet and the development of clinically detected CHF is an important next step in determining best treatment practices for the prevention of CHF.

Few longitudinal studies have evaluated the role of individual foods or dietary patterns in relation to CHF. Mozaffarian et al., reported that baked or broiled fish, but not fried fish, was inversely associated with CHF incidence in a group of elderly individuals free of CHF at baseline (25). This study also noted that plasma phospholipid n-3 FA, which correlated with baked/broiled fish but not fried fish, were inversely associated with CHF (25). An important role of oxidative stress in CHF pathogenesis has been hypothesized (26), as has been elevated plasma homocysteine concentration (27-30). Consequently, it is possible that foods rich in folate or other nutrients with significant antioxidant properties (e.g., vitamin E, vitamin C, selenium, zinc) may reduce risk of CHF or its complications. The final report of the Lyon Diet Heart study provides suggestive evidence that a Mediterranean style diet rich in omega-3 fatty acids and micronutrient-rich fruits and vegetables may effectively reduce risk of various cardiovascular diseases in persons with a history of myocardial infarction, CHF among them (31). However, more studies investigating the role of foods and diet patterns in the development of CHF are needed, especially those adequately designed to evaluate temporal relations.

(*for references, see page 5*)

5. Hypotheses:

1. Nutrients such as potassium, calcium, magnesium, and folate and omega-3 fatty acids will be associated inversely with incident CHF
2. Similarly, foods rich in the above nutrients, such as low-fat dairy products, fruits, vegetables, whole grains, and fatty fish will be associated inversely with incident CHF
3. A composite dietary score based on the above foods will show an inverse correlation with incident CHF whereas a composite dietary score reflecting a more sodium- and saturated-fat rich "Western" diet (refined grain foods, red meats, high fat dairy foods, and fried foods) will be positively associated with incident CHF.

6. Data:

EXCLUSIONS:

- Participants with previous history of heart failure at baseline
- Participants who were neither White nor African American at two centers
- African American participants from MN and MD centers (due to small numbers)
- Participants with inadequate measures of dietary intake (>10 missing items on food frequency questionnaire or kcal intake <600 or >4,200 for men or <500 or >3,600 for women)

EXPOSURES VARIABLES:

Nutrients
Food/food group servings/d
Dietary pattern score
Both continuous and categorical (as quartiles or quintiles) analyses will be considered
Note: To take advantage of the repeated measures of diet, exposures will be based on cumulative average diet: Specifically, between baseline and exam 3, dietary exposures will be based on diet as measured at the baseline exam. After exam 3, dietary exposures will be based on the mean of baseline diet and exam 3 diet (32).

OUTCOME VARIABLES:
Incident CHF defined according to hospital discharge records during follow-up

STATISTICAL ANALYSIS:
Data will be analyzed using Cox proportional hazards regression (SAS 9.1, PROC TPHREG). Risk of incident CHF will be calculated according to population-dependent categories (quartiles or quintiles) of dietary exposure variables using the lowest category as the referent. In continuous analyses, hazard estimates will be interpreted as risk of developing CHF per 1 standard deviation change in the exposure variable. It is anticipated, the more emphasis will be placed on the results of the categorical analyses.

Note: we acknowledge the substantial degree of intraindividual variability in dietary measures and the limitations this presents. We also understand that use of quartiles/quintiles merely shifts the error associated with analysis from that of random measurement error to that of differential exposure bias.

CONFOUNDERS/MODEL COVARIATES:
1. Main model (demographics + lifestyle variables): age (y), race/study center (W in MN, AA/W in MD, AA/W in NC, AA in MS), education (categorical), energy intake (kcal/d), smoking status (current/former/never and cigarette y), physical activity (Baecke score), multivitamin supplement use (y/n)

2. Above + prevalent disease at baseline: CHD, stroke, type 2 diabetes, use of hypertension medications (proxy for diagnosed hypertension)

3. Above + other potential mediators: BMI (kg/m^2), HDL-C (mg/dL), LDL-C (mg/dL), systolic BP (mmHg)

3b. Same model as 3 above, but instead using *time dependent covariates* for each BMI, HDL-C, LDL-C, and SBP + including also incident CHD, incident stroke, incident type 2 diabetes (also as *time dependent covariates*)

TESTING POTENTIAL INTERACTIONS:
Interaction between dietary exposures and baseline disease status and race group will be tested. Significance will be determined from the main model (model 1) including cross product terms (X dietary exposure*Y disease status and X dietary exposure*race group). Stratified analyses will be presented if risk estimates appreciably differ by baseline disease status or race group:

- Hypertension (use of medications for hypertension)
- Type 2 diabetes (fasting glucose >126mg/dL, self-reported diabetes, or taking meds for diabetes)
- CHD
- Stroke
- Obesity (BMI ≥ 25 kg/m^2)

- Race (W/AA)

MODEL INTERPRETATION:
Results of model 2 will be interpreted as the 'effect' of diet independent of demographics and lifestyle confounders, but not independent of dietary 'effects' on conditions and diseases such as obesity, hypertension, type 2 diabetes, and CHD/stroke

Results from models 3 and 4 will be interpreted as the 'direct effect' of diet on CHF, owing to factors that are independent of known impact of diet on the development of obesity, type 2 diabetes, CHD/stroke, and hypertension.

Note: In single nutrient/food analyses, other potential nutrient/food confounders will be considered, but results will be interpreted with caution given the potential for high collinearity among nutrients/foods.

7.a. Will the data be used for non-CVD analysis in this manuscript? No
7.b. NA

8.a. Will the DNA data be used in this manuscript? No
8.b. NA

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.
There is no overlap between this proposal and current proposals/published manuscripts.

10. What are the most related manuscript proposals in ARIC?
#922: *Alcohol consumption and risk of congestive heart failure*
Lead author: Louise Henderson

#927: *Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort*
Lead author: Wayne Rosamond

#1125: *Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study*
Lead author: Laura Loehr

#1160: *Life Course Socioeconomic Exposures and Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study*
Lead author: C. Roberts

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use any ancillary study data? No
11.b. NA

12. 1-3 year completion expectation: Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.

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