1.a. Full Title: Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and risk of coronary heart disease and ischemic stroke among individuals with hypertension in the Atherosclerosis Risk In Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): DASH diet and CHD, stroke

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

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4. Rationale:

We know that adherence to the Dietary Approaches to Stop Hypertension (DASH) diet lowered blood pressure over two months [1]. However, the effect of the DASH diet on risk of coronary heart disease (CHD) and stroke is not well understood, especially among adults with hypertension. Should physicians who are able to control a patient’s hypertension with medication still advise that patient to follow the DASH diet to lower their risk of CHD and
stroke? The DASH diet emphasizes high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, and low intake of sweetened beverages, red and processed meats, and sodium. Many of these foods influence risk of cardiovascular disease and therefore following this dietary pattern may be beneficial, even for patients who are already controlling their blood pressure with medication.

The benefits of reducing sodium (through reduction in blood pressure) are established [2], but whether reduced sodium intake in individuals with controlled hypertension is beneficial remains unknown. The effect of blood pressure on risk of cardiovascular disease is continuous and each mm Hg decrease in blood pressure is important [3-5]. Therefore individuals with controlled hypertension may still benefit by following the DASH diet if it lowers their blood pressure further. Some recent evidence also suggests that lowering sodium intake among individuals with prehypertension directly affects risk of cardiovascular events [6]. This study found that participants who were randomized to reduce their sodium intake for 18 months during the trials of hypertension prevention (TOHP) had fewer cardiovascular events 10-15 years later [6].

Additionally, several foods emphasized by the DASH diet are rich in nutrients that may reduce risk of cardiovascular disease through alternate mechanisms. For example fiber [7], potassium [7, 8], magnesium [7], folate [9, 10], and antioxidants [11, 12] are associated with risk of CVD and are found in fruits, vegetables, and whole grains. Other foods emphasized by the DASH diet like low-fat dairy contain low levels of saturated fat which increases risk of cardiovascular disease. And the DASH diet recommends avoiding red and processed meats which contain high levels of saturated fat. Some evidence suggests that higher dairy intake is associated with a reduced risk of stroke [13]. Previous studies also support the possibility that fruits, vegetables [14, 15] and whole grains [16] reduce risk of stroke. Whole grains, fruits, and vegetables may also reduce risk of incident coronary artery disease [17]. And a recent meta-analysis found that processed but not red meats were associated with an increased risk of CHD but not stroke [18]. Finally, a diet that includes several influential nutrients may have the largest impact on cardiovascular disease risk. Therefore it makes sense to study the effect of the DASH diet pattern rather than individual nutrients in isolation.

Previous research found that a DASH-like diet was inversely associated with risk of CHD in women with hypertension in the Nurses’ Health Study cohort [19] and inversely associated with risk of stroke in men and women with hypertension enrolled in the NHANES III follow-up study [20]. And interestingly, Fung et al. found that the protective effect of the DASH-like diet on risk of CHD was stronger in women with a history of hypertension compared to women without a history. A third study found that men and women with hypertension who were randomized to follow the DASH diet had an 18% reduced risk of CHD, estimated using the Framingham risk score equation [21].

Methods of creating the DASH diet

The DASH diet, advises individuals to achieve the following daily nutrient goals (for a 2,100 calorie eating plan) [1, 22]: 27% of calories from total fat, 26% of calories from saturated fat, 18% of calories from protein, 55% of calories from carbohydrate, 150 mg cholesterol, 2,300 mg sodium (1,500 mg sodium was a lower goal tested and found to achieve an even greater reduction in blood pressure), 4,700 mg potassium, 1,250 mg calcium, 500 mg magnesium, and 30 g fiber. However, because few individuals completely follow the DASH
diet, observational studies typically categorize individuals according to adherence to a DASH-type diet instead.

In the Nurses’ Health Study (NHS), a DASH–like diet score was calculated from reported intake of fruits, vegetables, nuts and legumes, low-fat dairy products, whole grains, sweetened beverages, red and processed meats, and sodium [19]. The NHS questionnaire did not ask any specific questions about sodium intake. Sodium intake was estimated using portion size and food composition data. Since sodium intake is highly variable, and because the questionnaire did not probe for sodium intake, measurement error for sodium intake in this study is likely substantial. After categorizing intake of each food/food group into quintiles, women were assigned a score of 1 if they fell in the lowest quintile of the following food groups (fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains) and 5 if they fell in the highest quintiles. Reverse coding was used for sodium, sweetened beverages, and red and processed meats. Component/food group scores were summed to obtain an overall DASH-like diet score where higher scores indicate better adherence to a DASH-like diet.

Parikh et al. [20] used a single 24-hour recall to measure diet in NHANES III and systematically probed for sodium intake by asking questions about salt added during food preparation, regular vs. lower sodium products, high sodium ingredients, and brand names [23]. They constructed a 9 point DASH-like diet score by assigning a score of 1 if participants met the DASH nutrient goal for each of 9 nutrients (fiber, cholesterol, calcium, magnesium, sodium, potassium, % calories from total fat, % calories from saturated fat, and % calories from protein). Participants received a score of 0.5 if they met an intermediate target (halfway between the population mean for that nutrient and the DASH target). Otherwise if participants did not meet the DASH target or the intermediate target they were assigned a score of 0 for that nutrient. Points for each of the 9 nutrients were summed to calculate an overall DASH-like diet score for each participant. Participants with a score greater than or equal to 5 were classified as DASH-like consumers and those with a score less than 5 were classified as typical diet consumers.

Chen et al. randomized participants with hypertension or prehypertension (systolic blood pressure > 160 mm Hg and diastolic blood pressure between 80 and 95 mm Hg) who were not taking antihypertensive medication to follow either a control diet, a diet that emphasized fruits and vegetables, or the DASH diet (described in detail above) [21]. All meals were prepared in research kitchens. They used the Framingham risk score equation to estimate risk of CHD. This equation uses information about systolic blood pressure, total cholesterol, HDL cholesterol, smoking, age, and sex to estimate 10-year risk of CHD.

The ARIC study uses a 66-item food frequency questionnaire (FFQ) to measure dietary intake. FFQ’s are often criticized as poor measures of dietary intake. For example, sodium intake is very difficult to measure with any accuracy using self-report (FFQ’s 24-hour recalls or food records). Instead, sodium should be measured using a 24-hour urine. However, individuals who report higher intake of processed meats and foods are likely to have higher sodium intake on average. Therefore a FFQ may be able to distinguish between individuals with very high and very low sodium intake.

The misclassification introduced by using a FFQ is likely nondifferential, and therefore would bias results towards the null, making it harder to detect small but existing associations. Despite this misclassification, Fung et al. were able to detect an association between a DASH-like diet and CHD using a FFQ [19]. And associations between diet measured by the ARIC FFQ and chronic diseases have been found in previous studies [17, 24, 25]. In addition, Parikh
et al. used a single 24-hour dietary recall which does not measure usual dietary intake, but was still able to detect an association with CHD [20].

Randomized trials typically do not follow participants long enough to study endpoints like CHD and stroke, therefore the ARIC cohort is an ideal study population for this research question. Other strengths of the ARIC cohort are the inclusion of both men and women, blood pressure obtained at each of four clinical exams (seated blood pressure was measured three times and the last two measures were averaged), the collection of antihypertensive medication use data (by questionnaire and in-person interviews), the 66-item FFQ was administered twice during follow-up (FFQs measure usual dietary intake vs. a single 24-hour recall which does not), and a large number of CHD and stroke events. Finally, since ARIC participants were age 45-64 at enrollment, a large number of participants have hypertension (2,562 at baseline and many more participants likely developed hypertension during follow-up).

5. Main Hypothesis/Study Questions:
   1. Among individuals using antihypertensive medication, do adults consuming a DASH-type diet have a lower risk of ischemic stroke than those consuming other diet patterns?
   2. Among individuals using antihypertensive medication, do adults consuming a DASH-type diet have a lower risk of CHD than those consuming other diet patterns?

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 use the ARIC cohort to conduct a prospective cohort study of diet and risk of CHD and stroke among adults using antihypertension medication over the 15 years of follow-up. We will exclude participants with previous or existing CHD or stroke at baseline. Our analysis will be restricted to participants using antihypertensives at exams 1, 2, or 3, since dietary data was collected at both visit 1 and 3.

   It is likely that only a small percentage of participants completely follow the DASH diet. Therefore we will categorize participants into quartiles of DASH-type diet score. Added salt intake was not obtained in the ARIC FFQ interview. We know that self-reported dietary intake will underestimate sodium intake; however, sodium is a natural component of foods, therefore, we will capture naturally occurring sodium intake. We will use Cox proportional hazards regression to evaluate the relation of dietary pattern with risk of stroke or CHD among individuals on medication for hypertension.

   We estimate that we have 82% power to detect a HR of 1.2 for our main analysis. This estimate is conservative since it uses only those participants who were hypertensive at baseline. We expect that several more study participants developed hypertension by visit 3 (when the second FFQ was administered) which will increase our sample size, and therefore power. We will additionally do an exploratory analysis stratifying by degree of blood pressure control: controlled (BP < 140/90), borderline control (BP 120/80-139/89), hypertension stage 1 (BP ≥ 140/90 and < 160/100), and hypertension stage 2 (BP ≥ 160/100). We will also do an exploratory analysis stratifying by type of medication (beta-blockers, diuretics, ace-inhibitors, etc.) [26, 27].
**Exposure variables:** dietary intake including % of calories from total fat (P.TFAT), % of calories from saturated fat (P.SFAT), % of calories from protein (P.PROT), % of calories from carbohydrates (P.CARB), mg cholesterol (CHOL), mg sodium (SODI), mg potassium (POTA), mg calcium (CALC), mg magnesium (MAGN), and g fiber (DFIB).

We will create a DASH-type pattern score by categorizing intake of each nutrient into quintiles. Participants will receive a score of 0-4 for quintiles 1-5. For % calories from total fat, % calories from saturated fat, % calories from carbohydrates, cholesterol, and sodium, participants will receive a score of 4 if they are in the lowest quartile and 0 if they are in the highest. For % calories from protein, potassium, calcium, magnesium, and fiber) participants will receive a score of 4 if they are in the highest quintile and 0 if they are in the lowest. A total DASH-type score will be calculated by summing across all nutrients.

**Outcome variables:** CHD, ischemic stroke

**Confounding factors:** age, sex, race, field center, education, energy intake, BMI, waist-to-hip ratio, smoking, physical activity, alcohol, estrogen use, multivitamin use, medications (antihypertension medications, type of antihypertension medication i.e. beta-blockers, diuretics, etc.).

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 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](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/

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.


25. Weng, L.-C., et al., Consumption of dairy products of a Mediterranean-type dietary pattern is inversely associated, whereas red and processed meat consumption is positively associated with incidence of hypertension in the Atherosclerosis Risk in Communities (ARIC) Study.
