ARIC Manuscript Proposal # 2963

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1.a. Full Title:
Adherence to a DASH dietary pattern and risk of Abdominal Aortic Aneurysm. Results from the Atherosclerosis Risk in the Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): DASH Diet and Abdominal Aortic Aneurysm

2. Writing Group:

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I, *Bernhard Haring* (the first author), confirm that all the coauthors have given their approval for this manuscript proposal.

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3. July 2010 NHLBI workshop at Northwestern University
The first author has participated in the July2010 NHLBI workshop at Northwestern University.

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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4. Timeline / Analyses
Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized. The expected timeline is 2017-2018.

5. Rationale

Abdominal aortic aneurysms (AAAs) are found in up to 8% of men aged >65 years. Although at most times they remain asymptomatic, rupture of an AAA carries high mortality. Among life-style modifiable risk factors for developing an abdominal aortic aneurysm smoking, hypertension, abnormal blood lipids and a diet high in saturated fat have been identified.[1-4] On the other hand, dietary studies suggest an inverse association between consumption of fruits as well as moderate alcohol consumption with AAAs but findings are inconsistent across studies.[1, 4-6] Evidence is lacking with regard to the association between dietary patterns and AAA prevention. Analysis of dietary pattern, which examines the effects of an overall diet and not just individual nutrients, may be a more informative approach given that nutrients are likely to have additive or synergistic effects.[7] Moreover, recommendations regarding various dietary patterns may be easier to implement in the general population.

The DASH (Dietary Approaches to Stop Hypertension) diet is a dietary pattern promoted by the National Heart, Lung, and Blood Institute, by the United States Department of Agriculture and the American Heart Association/American College of Cardiology as one healthy eating plan for all Americans.[8-10] It has been shown to effectively reduce blood pressure levels and improve blood lipids.[9, 11] Consequently, adhering to a DASH dietary pattern has been shown to effectively reduce cardiovascular events and the risk for kidney disease.[12-14]

The objective of this study is to assess if the recommendation of adhering to a DASH dietary pattern can also be extended to the prevention of incident AAAs. We therefore aim to examine the association between adherence to DASH-style dietary pattern and subsequent risk for AAA in a large, community-based cohort of middle-aged adults.

6. Research Hypothesis

The primary objective of this study is to evaluate the relationship between adherence to a DASH dietary pattern and the risk of incident AAA in a large, community-based cohort of middle-aged adults. We hypothesize that adhering to a DASH dietary pattern will be associated with a decreased risk for incident AAA.

7. Design and analysis

Study Population

The Atherosclerosis Risk in Communities Study (ARIC) is a community-based prospective cohort study of 15,792 middle-aged adults (aged 45-64 years at baseline) from four U.S. communities.[15] For this analysis, only white and black adults will be included; blacks from the Minneapolis and Washington County field centers will be excluded due to small numbers. We will exclude individuals with a previous diagnosis of AAA (reporting prior AAA surgery or aortic angioplasty) and those whose follow-up AAA status was uncertain (n = 28).[4, 16] Participants with incomplete dietary information or with extreme calorie intake (<600 kcal or > 4200 kcal per day for men, <500 kcal or > 3600 kcal per day for women) will also be excluded from the analysis.

Assessment of dietary intake

The ARIC study assessed foods intakes using an interviewer-administered, 66-item food frequency questionnaire (FFQ) adapted from the 61-item FFQ developed by Willett et al.[17] The FFQ was administered in person to all subjects by a trained interviewer at visit 1 at baseline (1987–1989) and at visit 3 (1993–1995). The FFQ has been reported to show good

reliability.[18] For analysis, the cumulative average diet of both measurements will be incoroporated, as this improves the usual dietary intake relative to a single assessment.[19]

Definition of DASH Diet Score

Adherence to a DASH-style diet will be assessed using a previously developed dietary scoring system.[14] Specifically, the DASH diet score used for this analysis considers intake of 1. fruits, 2. vegetables, 3. nuts and legumes, 4. low-fat dairy, 5. whole grains, 6. sodium, 7. sweetened beverages, and 8. red and processed meats.[14, 20] For fruits, vegetables, nuts and legumes, low-fat dairy, and whole grains, participants in the highest quintile will receive a score of 5, those in the second highest quintile received a score of 4, and so on. For sodium, sweetened beverages, red and processed meats, scoring will be reversed, i.e. individuals in the highest quintile will receive a minimum score of 1 whereas persons in the lowest quintile will receive a maximum score of 5. The score for each component will be summed and the overall score ranges from 8 (no adherence) to 40 (perfect adherence). Study participants did not receive dietary counseling, and the DASH diet results were not published at the time of ARIC study visits.[9]

Assessment of abdominal aortic aneurysm (AAA)

The primary endpoint for this study will be incident AAA after ARIC visit 1. ARIC identified incident AAAs by several strategies as previously outlined.[4, 16] In the annual telephone calls with ARIC participants, interviewers asked about any interim hospitalizations and identified deaths, and these records were sought. ARIC also conducted surveillance of local hospitals to identify additional hospitalizations or deaths. In addition, ARIC linked participant identifiers with Medicare data from the Centers for Medicare and Medicaid Services (CMS) for 1991–2011, to find any missing hospital or outpatient events for those over 65 years. Clinical AAAs were identified as those with a hospital discharge diagnosis from any source, or two Medicare outpatient claims that occurred at least one week apart, with ICD-9-CM codes of 441.3 or 441.4, or procedure codes of 38.44 or 39.71, or the following cause of death codes: ICD-9 441.3 or 441.4 or ICD-10 code I71.3 or I71.4.[4] Although labeled “clinical AAAs” these diagnoses would include both symptomatic and asymptomatic AAAs that were medically documented. Thoracic, thoracoabdominal, or unspecified aortic aneurysms will be treated as non-events.

To identify additional asymptomatic AAAs in the surviving ARIC cohort in 2011–2013, a screening abdominal ultrasound in the fifth ARIC examination was performed by centrally trained sonographers.[16] Images of anterior-posterior and transverse diameters at the proximal aorta just below the superior mesenteric artery, the proximal infrarenal aorta 2 cm below the renal arteries, the distal infrarenal aorta 1 cm above the bifurcation, and the point of maximal infrarenal aortic diameter were acquired. Furthermore, a longitudinal view of the infrarenal aorta was taken. To identify all AAAs ≥ 3 cm, vascular imaging physicians reviewed any image that the sonographers judged had > 2.8 cm maximal infrarenal diameter or probable pathology, plus a 5% random sample of the rest.

Covariates

In the ARIC study, height, weight, and waist circumference were measured following a standardized protocol.[15, 21] ARIC participants underwent fasting venipuncture at each examination.[15] Data on smoking status (current, former, never), education, intake of antihypertensive or lipid lowering medication were derived from standardized

questionnaires.[15] Pack-years of smoking were calculated as the average number of cigarettes smoked per day multiplied by the years of smoking divided by 20 (the number of cigarettes in a standard packet). We defined longitudinal smoking status based on smoking behavior ascertained from Visit 1 to Visit 4 (or Visit 3 if smoking information in Visit 4 was missing) as follows: Never smokers (defined as never smoker from Visit 1 to Visit 4), quitters before Visit 1 (former smoker at Visit 1 and not smoking at Visit 2 to Visit 4), recent quitters (current smoker at Visit 1 and non-smoker from Visit 2 to Visit 4), and continuous smokers (current smoker from Visit 1 through Visit 4 allowing for "former smoker" status only once between Visit 2 to Visit 4).[4] Sports-related physical activity and leisure related physical activity were assessed with the use of Baecke's questionnaire and scoring systems.[22] Hypertension will be defined as the average of the last two of three blood-pressure readings at the first visit (using 140mmHg or higher for systolic and 90mmHg or higher for diastolic as cut-off points). Diabetes status will be coded positive in individuals with self-reported diabetes, fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL or use of diabetes medication.

Statistical Analysis

Mean values for continuous variables and proportions for categorical variables will be used to describe baseline characteristics (ARIC visit 1, 1987-1989) according to tertiles of DASH dietary score (Table 1).

To assess the association of DASH dietary scoring with AAA (Table 2), we will calculate incidence rates (IR) of outcome events per 1000 person-years as the number of diagnosed cases of AAA cases occurring during the entire follow-up period divided by person-years of follow-up. Person-years of follow up will be defined as time from the baseline examination to the date of the first outcome event, death, lost to follow-up, or December 31, 2011. Thereafter, corresponding rate ratios will be calculated by dividing the rate among participants in each specific intake tertile by the rate among participants in the lowest qtertile of intake (reference). Cox proportional hazards regression models will be used to account for potential confounding. An initial model will adjust for age, race, sex, education, ARIC study center, and total energy intake (minimally adjusted model). A second model will additionally adjust for smoking status (current, former, never), pack years of smoking, systolic blood pressure (mmHg), use of antihypertensive medication, HDLc (mmol/l), diabetes status, total cholesterol (mmol/l), use of lipid lowering medication, body mass index (kg/m^2), height, ethanol intake, Baecke's physical activity score and leisure-related physical activity (fully adjusted model). Besides examing the overall dietary pattern, we will also examine the relationship between individual components of the DASH diet score and risk for AAA, modelling all factors in the fully adjusted model (Table 3). In sensitivity analyses, we will further investigate the association of refined grains and and risk for AAA.

To characterize the distribution of dietary sources of a DASH dietary pattern, we will plott frequency histograms. In addition, to visualize the continuous association between adherence to a DASH dietary pattersn as well as individual dietary sources with risk of incident AAA, we will plot linear splines with two knots, corresponding to the tertiles (Figure). The 10th percentile of dietary intake will be used as the reference point in all spline models. We will truncate the data at the 99th percentile to minimize the influence of extreme values.

Finally, we will test for effect modfification by demographic factors (sex and race), socioeconomic status (education level), and clinical characteristics (overweight/obese status,

diabetes status, and hypertension status) using stratified analyses and tests of interaction with each of the potential modifiers (Figure).

8. Conclusion

We anticipate that adhering to a DASH dietary pattern will be associated with a lower risk for AAAs. We expect individual dietary components such as red and processed meat will be associated with an increased risk for AAA whereas food items such as low-fat dairy, nuts and legumes will be associated with a reduced risk of AAA.

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

9.b. NA

10.a. Will the DNA data be used in this manuscript? No

10.b. NA

11.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. Yes

12. 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)?

13. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

AS 2009.18: "Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm", *R01HL103695, PI Weihong Tang*

14a. 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.

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.

14.b. 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.

Yes, the lead author is aware of the Public Access Policy and that manuscript has to be uploaded to Pubmed Central.

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Table 1. Baseline characteristics according to Tertiles of DASH diet score, ARIC 1987-1989

	Tertile 1: Score (n=xxx)	**Tertile 2: Score (n=xxx)**	**Tertile 3: Score (n=xxx)**	**P-value for linear trend**
Age, years				
Female, %				
Black, %				
Current cigarette smoker, %				
Pack-years (smoking)				
Education, %				
Less than high school				
High school or equivalent				
College or above				
Systolic blood pressure, mmHg				
Hypertension, %				
Anti-hypertensive medication, %				
Total cholesterol, mg/dL				
LDL cholesterol, mg/dL				
Triglycerides, mg/dL				
HDL cholesterol, mg/dL				
Lipid-lowering medication, %				
Body mass index, kg/m^2				
Leisure index				
Physical activity index				
Total caloric intake, kcal/day				
Alcohol intake, g/wk				
Total protein intake, g/day				

Total protein intake, %kcal
Animal protein intake, g/day
Vegetable protein intake, g/day
Total carbohydrate intake, g/day
Carbohydrate intake, %kcal
Total fat intake, g/day
Total fat intake, %kcal
Saturated fat intake, g/day
Polyunsaturated fat intake, g/day
Monounsaturated fat intake, g/day
Dietary fiber, g/d

ARIC, Atherosclerosis Risk in Communities Study; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein

[a] Food consumption will be estimated using cumulative average intake. For those who developed AAA or were censored from the analysis before visit 3, food frequency questionnaire data from visit 1 will be used. Otherwise, for those who developed AAA or were censored from the analysis after study visit 3, the average of food frequency questionnaire data from visits 1 and 3 will be used

Table 2. Association of Tertiles of DASH diet score with incident AAA

	Tertiles DASH Diet score [a]			P-value for linear trend
	Tertile 1 (low)	**Tertile 2 (moderate)**	**Tertile 3 (high)**	
Person-years				
Events				
Score Range				
HR (95% CI)*	1 (ref)			
HR (95% CI)†	1 (ref)			

ARIC indicates Atherosclerosis Risk in Communities Study; CI, confidence interval; HR, hazard ratio.

[a] Food consumption will be estimated using cumulative average intake. For those who developed AAA or were censored from the analysis before visit 3, food frequency questionnaire data from visit 1 was used. Otherwise, for those who developed AAA or were censored from the analysis after study visit 3, the average of food frequency questionnaire data from visits 1 and 3 will be used.

*Model 1: Adjusted for age, race, ARIC center, sex, education level, and total caloric intake.

†Model 2: Adjusted for variables in model 1 + high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, total cholesterol, lipid-lowering medication use, systolic blood pressure, anti-hypertensive medication use, ethanol intake, smoking status, pack years of smoking, physical activity index, leisure-related physical activity, body mass index, and height.

Table 3. Association of Individual DASH components and risk for AAA

Component	Quintiles of DASH components [a]			P-value for linear trend
	Tertile 1 (Low Intake)	Tertile 2	Tertile 3 (High Intake)	
Sodium				
Person-years				
Events				
Median, g/d				
HR (95% CI)*	1			
HR (95% CI)†	1			
Red and processed meat				
Person-years				
Events				
Median, svg/d				
HR (95% CI)*	1			
HR (95% CI)†	1			
Sweetened beverages				
Person-years				
Events				
Median, svg/d				
HR (95% CI)*	1			
HR (95% CI)†	1			

Fruits	
Person-years	
Events	
Median, svg/d	
HR (95% CI)*	1
HR (95% CI)†	1
Vegetables	
Person-years	
Events	
Median, svg/d	
HR (95% CI)*	1
HR (95% CI)†	1
Whole grains	
Person-years	
Events	
Median, svg/d	
HR (95% CI)*	1
HR (95% CI)†	1
Low-fat dairy	
Person-years	
Events	
Median, svg/d	
HR (95% CI)*	1
HR (95% CI)†	1
Nuts and legumes	
Person-years	
Events	

Median, svg/d	
HR (95% CI)*	1
HR (95% CI)†	1

ARIC indicates Atherosclerosis Risk in Communities Study; CI, confidence interval; HR, hazard ratio; and svg/d, servings/day.

[a] Food consumption will be estimated using cumulative average intake. For those who developed AAA or were censored from the analysis before visit 3, food frequency questionnaire data from visit 1 will be used. Otherwise, for those who developed AAA or were censored from the analysis after study visit 3, the average of food frequency questionnaire data from visits 1 and 3 will be used.

*Model 1: Adjusted for age, race, ARIC center, sex, education level, and total caloric intake.

†Model 2: Adjusted for variables in Model 1 + high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, total cholesterol, lipid-lowering medication use, systolic blood pressure, anti-hypertensive medication use, ethanol intake, smoking status, pack years of smoking, physical activity index, leisure-related physical activity, body mass index, and height.