# ARIC Manuscript Proposal # 1445

**PC Reviewed: 11/11/08** **Status: A** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Longitudinal relation between dietary intake and peripheral arterial disease in middle-aged adults: ARIC

**b. Abbreviated Title (Length 26 characters)**: **Dietary intake and PAD**

**2. Lead Author**: Lyn M. Steffen
**3.** Writing group members: Pamela Lutsey, Jackie Boucher (Abbott Northwestern), Abby Ershow (NIH), Alan Hirsch, Aaron Folsom, Lloyd Chambless

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

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**4. Timeline**:
literature review: 1 month
data analysis: 3-4 months
manuscript preparation: 6-8 months
total time: 1 year

**Rationale**:

In the U.S., peripheral arterial disease (PAD) affects 8-12 million adults 40 years of age or more, with similar proportions of men and women (1,2). PAD, caused primarily by atherosclerosis, is a blockage in the inner lining of a vital artery caused by fatty deposits, resulting in poor circulation (1). PAD in the lower extremity is commonly defined as resting ankle-brachial index (ABI; calculated as the systolic blood pressure in the right or left ankle divided by the average of the two brachial artery pressures) of less than 0.90.

Adherence to medication therapies and modification of lifestyle factors, including smoking cessation, healthy dietary intake, and increasing moderate physical activity, are important for the management of peripheral arterial disease (1). However, it is not clear whether dietary intake is important in the prevention of PAD.

*Dietary intake.* Few published studies have investigated the relation between dietary intake and risk of developing incident PAD. A cross-sectional study of the relation between nutrient intakes and PAD reported lower odds of PAD with intakes of vegetable oil (ie, olive oil, canola oil) in the highest quartile (greater than or equal to 34.4 gm/day) compared to the lowest quartile (range not reported in the article)(OR 0.39; 95% CI 0.16, 0.97); and vitamin E intake in the highest quartile (greater than or equal to 7.7 mg/day) compared to the lowest quartile (range not reported in the article) (OR 0.37; 95% CI 0.16, 0.84) (3). The main vegetable fat consumed in this study was olive oil, which is rich in both monounsaturated and polyunsaturated fatty acids as well as flavonoids and terpenes. It is known that polyunsaturated fatty acids favorably influence serum cholesterol concentrations and endothelial function (4), while flavonoids and terpenes function as antioxidants (5). Vitamin E, found mainly in cooking oils, also contains antioxidant and anti-inflammatory properties and inhibits platelet aggregation (6). In a case-control study of antioxidant intake and PAD, lower vitamin C intake was reported in PAD cases compared to controls (7). Lower levels of ascorbic acid and higher CRP levels were observed in PAD patients compared to those in hypertensives or healthy controls (8). It is possible that intakes of vegetable oil (ie, olive oil), vitamin E, and vitamin C are markers for the Mediterranean diet pattern, which has been associated with lower risk of chronic disease in numerous studies (9-11).

In epidemiologic studies, low to moderate alcohol intake is inversely associated with PAD, CVD, and type 2 diabetes (12-14). Alcohol may promote beneficial effects on CVD and risk factors through changes in lipids, hemostatic factors and fibrinolysis, inflammatory markers, and glucose control parameters (13). In addition, intake of 1-2 servings of fish per week is associated with greater vascular health (15). There are no longitudinal studies examining the relation between dietary intake, including nutrients, foods, and diet patterns, and risk of developing incident PAD.

**5. Main Hypothesis/Study Questions**:

**a.** Is dietary intake associated with risk of developing incident PAD over 13 years of followup?

**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).**

**EXCLUSIONS AT BASELINE**:

- Inadequate dietary intake information or extreme energy intake
- Participants with prevalent PAD
- Missing covariates
- Participants who are not white or African-American

**EXPOSURE VARIABLES**:

Food groups and subgroups will be created using baseline and visit 3 food and frequency/serving size data as well as the following nutrient data: vitamins C and E, folate, fatty acids, including saturated, monounsaturated, and polyunsaturated fat, dietary fiber, and alcohol. Food groups include whole grain foods, refined grain foods, fruit, nuts, vegetables, dairy, meat, coffee, etc. Subgroups of major food groups will be created: for example, meat subgroups include red and processed meat, poultry, and fish. The average of baseline and visit 3 nutrient and food intakes will be used to increase precision of dietary intake (16).

Diet patterns, such as the western diet pattern, will be created using principal components analysis. A Mediterranean pattern score will be created according to the method used by Dr. Chambless in a previous paper. A value of 0 or 1 was assigned to each of nine indicated components with the use of the sex-specific median as the cutoff.

- For beneficial components (vegetables, legumes, fruits and nuts, whole grain foods, and fish), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1.
- For components presumed to be detrimental (meat, poultry, and dairy products), persons whose consumption was below the median were assigned a value of 1, and persons whose consumption was at or above the median were assigned a value of 0.
- For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g per day and to women who consumed between 5 and 25 g per day.
- For fat intake we used the ratio of monounsaturated + polyunsaturated fats to saturated fats, above the median taken as a beneficial intake.

Our Mediterranean diet score is similar to that of Trichopoulou (17), except that we separated nuts and fruits, we replaced the cereal category by whole grains, we combined meat and poultry, and for fat we used the ratio of monounsaturated plus polyunsaturated fats to saturated fats (instead of the ratio of monounsaturated fats to saturated fats).

Confounding factors include age, sex, race, field center, HRT use, medication use (bp, lipids, diabetes meds), vitamin use, diabetes status.

**OUTCOME VARIABLES**:

- Incident PAD as defined by the following criteria: 1) a new ankle-brachial index (ABI) measure of < 0.90 at either visit 3 or 4; 2) new intermittent claudication based on the Rose questionnaire; or 3) a hospital discharge code for PAD, leg amputation, or leg revascularization procedures (leg endarterectomy, aorto-iliac-femoral bypass surgery, or leg bypass surgery)

**STATISTICAL ANALYSIS**:

In longitudinal analysis, Cox proportional hazards regression analysis will evaluate the relation between dietary intake (nutrients, food groups, and diet patterns) and incident PAD over 13 years of followup (through 2002). We will evaluate the relation between dietary intake and incident PAD, where dietary intake is the average of baseline and visit 3 measures and incident PAD is define above.

Limitations: An important limitation is the use of a food frequency questionnaire containing only 66-items (visit 1 and 3), thus restricting the number of food categories to characterize usual dietary intake which likely results in energy intake that is underestimated. Dietary intake may be misclassified by this questionnaire, contributing to measurement error in the point estimates that may potentially result in large biases either towards or away from the null (18). We will explore the effects of bias due to measurement error and will consider correction for that error (19,20).

**MODEL COVARIATES**:

Model 1. Adjusted for age, gender, race, field center, education, energy intake;
Model 2. Adjusted for model 1 plus physical activity, baseline smoking status, pack-years, vitamin supplement use, medication use, HRT, and simultaneous adjustment for other food groups (for food group models); for other nutrients (for nutrient models).
Model 3. Adjusted for model 2 plus physiological measurements (baseline systolic blood pressure and cholesterol).

**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 ICTDER02 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 ICTDER02 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 ICTDER02 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. primiarly 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.**

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