ARIC Manuscript Proposal #2245

PC Reviewed: 10/8/13       Status: A       Priority: 2
SC Reviewed: _________     Status: _____  Priority: ____

1a. Full Title: Lower extremity arterial disease and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Lower extremity arterial disease and cognitive decline

2. Writing Group:
   Writing group members: Priya Palta (lead), Michelle Snyder, A. Richey Sharrett, Alden Gross, Alvaro Alonso, Lisa Wruck, Corey Kalbaugh, Gerardo Heiss, others welcome
   * Tom Mosley has also been invited to participate

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. PP [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: Goal is to submit an abstract to the AHA-Epi conference (10/14/13). We anticipate that the full manuscript will be prepared within 9 months of manuscript proposal approval.

4. Rationale:

   The prevalence of dementia and cognitive impairment is high and increases significantly with age. Among adults 71-79 years, prevalence of dementia is estimated at 5.0% and rises to 40% among individuals 90 years of age and older.\(^1,2\) Most prior research on cardiovascular risk
factors for cognitive decline and dementia has focused on cardiovascular disease risk factors or cardiovascular disease manifestations, but not on subclinical cardiovascular disease. Prevalence estimates for stroke and heart failure in adults 65-74 years are 7% and 6%, respectively. Although the prevalence of clinical cardiovascular disease is high, the prevalence of subclinical cardiovascular disease in older adults is considerably higher at around 37%.

Because subclinical disease is (by definition) undiagnosed and untreated for up to several years, measures of subclinical cardiovascular disease are advantageous in avoiding a number of potential biases often induced by selection, diagnostic practices, treatment and behavior. Subclinical diseases have clinical and public health relevance in identifying individuals not yet symptomatic to reduce the risk of overt clinical disease. Subclinical cardiovascular disease is predictive of clinical cardiovascular disease and mortality. Identifying whether subclinical cardiovascular disease is associated with cognitive decline can additionally provide the opportunity to screen for and subsequently treat cognitive decrements before further mechanistic damage occurs with clinical disease.

Ankle-brachial index (ABI) is a measure of subclinical atherosclerosis frequently used in epidemiologic studies and recommended for use in clinical practice. As a subclinical marker of atherosclerosis, ABI is an indication of the long-term chronic progression of atherosclerosis and is primarily used as an index of lower limb Peripheral Arterial Disease (PAD). There has been limited research assessing the association between ABI and cognitive decline and impairment. Six cross-sectional studies and six longitudinal studies have been conducted to look at ABI and cognitive impairment and dementia. Among the cross-sectional studies, results consistently showed an association between lower ABI and cognitive impairment, but methodological limitations of the studies limit the generalizability of the findings. The Mini Mental State Examination test (MMSE) was the sole metric used to assess cognitive impairment in three of the studies. The MMSE is not sensitive to early or minor cognitive impairments due to its pronounced ceiling effects. Most longitudinal analyses examined ABI and risk of all-cause or cause-specific dementia, while only one study looked at ABI and cognitive impairment longitudinally. Similar to the cross-sectional studies, the MMSE was the most commonly utilized cognitive assessment. Although cognitive assessments differed across studies, the definition for a low ABI, indicated by an ABI <0.9, was consistently used across studies. Additionally, these studies had homogenous populations and lacked data to assess for racial differences. This is of particular concern considering the established racial differences in both measured cognitive function and the frequency of subclinical cardiovascular disease.

Considering the above limitations, the objective of this analysis is to estimate the longitudinal association of lower extremity arterial disease (indexed by ABI <0.9 and/or clinically manifest PAD documented by ICD-9 hospital discharge codes or self-report) with 20-year decline in three cognitive tests (Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale (test of executive function and psychomotor speed), Delayed Word Recall Test (test of memory), and Phonemic Word Fluency Test (test of language) in a bi-racial cohort of older adults.

5. Main Hypothesis/Study Questions:

Aim: To test the hypothesis that a low ankle-brachial index (ABI) or clinical manifestation of peripheral arterial disease (PAD) across ARIC visits 1-5 is associated with a greater 20-year decline in cognitive scores (from cohort exam visits 2-5).
Hypothesis #1: Compared to individuals without indication for lower extremity arterial disease (ABI $\geq 0.9$ and no clinical manifestation of PAD), individuals with lower extremity arterial disease (indexed by ABI $< 0.9$ and/or clinically manifest PAD documented by ICD-9 hospital discharge codes and/or self-reported diagnoses of PAD/revascularizations) will have a greater 20-year rate of decline in cognitive test scores.

Hypothesis #2: Among individuals with a manifestation of lower extremity arterial disease, those individuals with an earlier manifestation will have the greatest 20-year decline in cognitive test scores.

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).

Study design: Prospective analysis of lower extremity arterial disease and 20-year decline in cognitive test scores.

Exclusion: Prevalent stroke/TIA; not Caucasian or African-American; African-Americans not from Jackson or Forsyth; ABI $\geq 1.40$

Exposure:

Lower extremity arterial disease
- ABI $< 0.9$ in either the right or left leg measured anytime at visits 1-5
  
  *Note: ABI measurements from Visits 1 to 4 were measured on a single, randomly selected lower extremity. ABI measurements at Visit 5 were performed on both extremities.*

  and/or

- A clinical manifestation of peripheral arterial disease (PAD) anytime at visits 1-5 based on ICD-9 codes or self-report. ICD-9 codes for PAD as outlined by Corey Kalbaugh in MS#1832:
  
  1. ICD-9 diagnosis codes for symptomatic PAD: 443.9 (intermittent claudication, peripheral vascular disease not otherwise specified), 707.1-707.19 (lower extremity ulcers), 785.4 (gangrene)
  2. ICD-9 procedure codes for symptomatic PAD: 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 84.17 (above knee amputation), 38.18 (leg endarterectomy), 39.29 (leg bypass), 39.50 (leg angioplasty).
  3. Self-report of peripheral arterial disease at annual follow-up interviews (AFU)
  4. Self-report of revascularization of the lower extremities at AFU

No lower extremity arterial disease
- ABI $\geq 0.9$ in both the right and left legs indicates normal ABI and no lower extremity arterial disease
- No clinical manifestation of PAD
No self-report of PAD or revascularization of the lower extremities

Outcome:

20-year cognitive change: Cognitive decline will be assessed on three cognitive tests that have data available at Visits 2, 4, and 5 (ARIC-NCS): Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale (test of executive function and psychomotor speed), Delayed Word Recall Test (test of memory), and Word Fluency Test (test of language). To make relative comparisons across these domain tests, the raw test scores will be standardized in order to accommodate the differences in test units and scales. For each neuropsychological test, a z-score will be calculated based on the means and standard deviations at baseline (Visit 2). The 20-year decline will be calculated from first available cognitive measurement to Visit 5 ARIC-NCS.

Covariates/Potential Effect Modifiers: Age, education, sex, race/center, ApoE4, cigarette smoking, depression, hypertension, diabetes, blood cholesterol levels, cardiovascular diseases (coronary heart disease (CHD) and heart failure).

Analysis:

For Aim 1, the distribution of ABI and the prevalence of PAD will be described across ARIC visits. We propose the use of linear random effects models to examine 20-year declines in cognitive tests: Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale (test of executive function and psychomotor speed), Delayed Word Recall Test (test of memory), and Word Fluency Test (test of language). We will include effects for baseline intercepts and for rates of change in cognitive test scores over time. An interaction term between lower extremity arterial disease and time will be incorporated to model rates of change in cognitive test performance between those individuals with and without lower extremity arterial disease.

We will evaluate several models for our aims. Model 1 will adjust for demographic factors including age, education, sex, and race/center. Model 2 will include characteristics in model 1 and other disease factors associated with both cognitive decline and lower extremity arterial disease: ApoE4, depression hypertension, blood cholesterol levels and cardiovascular diseases (CHD and heart failure). Subsidiary analyses will further explore for effect modification by diabetes and smoking.

Attrition and selection biases are of concern when analyzing longitudinal cognition data. As proposed by the ARIC-NCS Analysis Committee, we will perform sensitivity analyses using inverse probability weighting to account for potential selection bias.

Methodological limitations: ABI measurements from Visits 1 to 4 were measured on a single, randomly selected lower extremity. Lower extremity arterial disease can be unilateral and may not be adequately captured with measurements in one extremity only. Identifying clinical manifestations of PAD through ICD-9 codes and self-report of revascularization will help to reduce misclassification of lower extremity arterial disease.

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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group? _____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)?

There are no known overlapping proposals examining ABI and cognition. There are some related manuscripts based on our proposed exposure or outcome:

MS575: Ankle-Brachial Index and Ischemic Stroke Incidence: The ARIC Study (lead: Albert Tsai)

MS324: Continuous Values of ABI: Risk Factors for Lower Extremity Arterial Disease, and Possible Gender Differences (lead: JJ Nelson)

MS1973: Cardiovascular exposures, cognitive decline and depression in whites and blacks (lead: Adina Zeki Al Hazzouri)

MS2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (lead: A Rawlings)

MS2201: Lipids, statins, and 20-year cognitive change: The ARIC-Neurocognitive Study (lead: M Power)
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? 

__X__ Yes    ____ No

Using ARIC-NCS data (2008.06-ARIC NCS)

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.cscn.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. Agreed

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.
References