ARIC Manuscript Proposal #2166

PC Reviewed: 7/9/13	Status: <u>A</u>	Priority: <u>2</u>
SC Reviewed:	Status:	Priority:

1.a. Full Title: Habitual physical activity and arterial stiffening

b. Abbreviated Title (Length 26 characters): Physical activity and PWV

2. Writing Group:

Hirofumi Tanaka, David Aguilar, Kunihiro Matsushita, Natalia Gouskova, Gerardo Heiss, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _HT_

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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: Analysis is to begin when the final ARIC dataset from the visit 5 becomes available. We plan to complete the manuscript within one year from release of the data.

4. Rationale:

Arterial stiffness exerts a number of adverse effects on cardiovascular function and is associated with mortality in patients with end-stage renal desease and essential hypertension ^{1,2}. Increased arterial stiffness can contribute to the development and progression of hypertension, left ventricular hypertrophy, ischemic heart disease, and congestive heart failure. The pathogenesis of arterial stiffening includes functional and

structural changes in the arterial wall, modulated in part by traditional risk factors for atherosclerotic vascular disease ^{3, 4}.

A first-line approach for prevention and delayed progression of cardiovascular disease is lifestyle modification including regular physical activity. A number of observational and interventional studies indicate that habitual exercise can prevent and reverse arterial stiffening ⁵⁻⁷, with the notable exception of the ARIC study that found no association between regular physical activity and arterial stiffness in community-dwelling adults ⁸. The reasons for the discrepant results, in addition to publication bias, may be related to the use of arterial distensibility in ARIC that does not account for local pulsatile pressure changes and/or the use of a questionnaire to estimate physical activity levels in a sample of mostly sedentary adults.

It is well established that habitual exercise is associated with improvements in conventional risk factors for cardiovascular disease in older adults⁹. However, more than 40% of the risk reduction associated with habitual exercise is unexplained by its effects on traditional risk factors¹⁰. It is conceivable that some of the beneficial effects of habitual exercise may be through mitigation of age-related vascular dysfunction or arterial stiffening in the presence of traditional risk factors. It is not known, however, whether arterial stiffness is lower in older adults with multiple risk factors who regularly engage in physical activity and/or possess high functional fitness.

The ARIC visit 5 examination provides an excellent opportunity to examine the association between regular physical activity/functional fitness and arterial stiffness in a community-based cohort of older adults, for several reasons. The best established measure of arterial stiffness, pulse wave velocity, was assessed as well as the short physical performance battery (SPPB), which can be considered, with or without physical activity levels estimated by the ARIC physical activity questionnaire, to provide objective measures of functional fitness.

5. Main Hypothesis/Study Questions:

- 1. We posit that carotid-femoral PWV (cfPWV) is inversely associated with habitual physical activity, and with functional fitness in men and women examined by the ARIC study as part of Visit 5. These associations will be linear and monotonic (without detectable thresholds).
- 2. The habitual physical activity and functional fitness are additive in their associations with cfPWV with those estimated for the history of hypertension, diabetes, and cigarette smoking.

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 methodological limitations or challenges if present).

Study design: The cross-sectional study sample will include individuals who participated in the ARIC visit 5.

Primary dependent variables: Arterial stiffness measures including carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), and carotid artery augmentation index.

Independent variables: Physical activity levels (work, leisure, and sports) will be estimated by the ARIC physical activity questionnaire, functional fitness as measured by short physical performance battery (SPPB), and covariates will include age, body mass index, diabetes, HDL-cholesterol and LDL-cholesterol, blood pressure, and smoking. Established risk factors for arterial stiffening to be considered by effect measure modification/ vs. additive effect estimation will be cumulative exposures to (each of) type 2 diabetes, hypertension and cigarette smoking.

Exclusions: Missing information on PWV, blood pressure, and antihypertensive medication use or other covariates of interest; and exclusions recommended by the ARIC ABI/PWV Working group: participants with BMI≥40, participants with major arrhythmias (based on ECG data), participants with ABI <0.9, reported use of antiarrhythmic or vasoactive medications per the ARIC medication survey use (MSR Item 33.g) and/or specific medication codes in the ARIC database.

Statistical Analyses:

Participant characteristics will be reported as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. If lack of normality is not a concern and transformation is not required then conventional statistics will be used. If normality is a concern we will use non-parametric methods.

Initially the associations between arterial stiffness and physical activity or functional fitness will be assessed using least squares estimates. Multivariable-adjusted regression analyses will be used by using adjustments for covariates (see above).

Limitations:

Some PWV measurements are missing due to technical errors, participant factors and scheduling conflicts. Physical activity is estimated using a questionnaire. Finally, the cross-sectional design limits our ability to determine causality.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes ____ Yes _____ 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 ____ 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

____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)?

#003A The relationship between CVD risk factors and carotid artery distensibility in middle-aged adults (Burke G)

#511 Physical activity and arterial stiffness (Folsom A)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____Yes __X__ No

*ancillary studies are listed by number at http://www.cscc.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.

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. <u>http://publicaccess.nih.gov/submit_process_journals.htm</u> shows you which journals automatically upload articles to Pubmed central.

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