ARIC Manuscript Proposal # 3238

PC Reviewed: 9/11/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Clinically recognized varicose veins and physical function in older individuals

b. Abbreviated Title (Length 26 characters): Varicose veins and physical function

2. Writing Group:

Writing group members: Yejin Mok, Junichi Ishigami, Anna Kucharska-Newton, Maya Salameh, Jennifer Schrack, Josef Coresh, Beverly G. Windham, Pamela Lutsey, Aaron Folsom, Kunihiro Matsushita

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

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3. Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Varicose veins of the lower extremities, which are manifestation of chronic venous insufficiency, has been estimated approximately 23% of adults in the US, and affect approximately 22 million women and 11 million men aged 40 to 80 years.[1] Varicose veins can progress to serious morbidity such as risk of leg ulcers[2] or be related to future risk of deep

venous thrombosis.[3-5] Also, the medical cost of chronic venous disease in the US have been reported to reach $3 billion per year, mostly due to advanced cases with leg ulcers.[2, 6]

An important clinical manifestation of varicose veins is leg symptom such as feelings of heaviness or tightness,[7] which may result in reduced leg function. Also, lower physical function has been reported as a risk factor of varicose veins.[8] Indeed, a few cross-sectional studies demonstrated the association between varicose veins and reduced physical function.[9-12] However, most of them were small (n<1000)[9-12] or examined limited measures of physical function (e.g., only walking,[9, 12] range of the ankle motion,[10] lower extremity muscle strength[11]). Therefore, we aim to quantify the cross-sectional association of varicose veins with comprehensive objective measures of physical function (e.g., the Short Physical Performance Battery and grip strength) and physical activity using data from visit 5 of the Atherosclerosis Risk in Communities (ARIC) Study. Since a few measures of physical function are included in the definition of frailty and frailty is an important concept for older adults, we will also analyze the association of varicose veins and frailty. In addition, combining visit 6 data, we will evaluate whether prior history of varicose veins at visit 5 is associated with subsequent changes in physical function.

5. Main Hypothesis/Study Questions:

- Varicose veins will be associated with lower physical function, lower physical activity, and frailty independently of comorbidities such as diabetes, hypertension, or history of cardiovascular disease.
- Since varicose veins tend to affect lower extremity, the associations will be more evident for lower extremity function (e.g., walking speed) than (i.e., grip strength).
- We will confirm these associations in longitudinal data from visits 5 and 6.

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:

1. Cross-sectional study
   We will quantify the cross-sectional association of varicose veins with physical function, physical activity and frailty using data from visit 5.
2. Longitudinal study
   We will utilize a longitudinal study design to assess the association of history of varicose veins at visit 5 with changes in physical function, physical activity and frailty from visit 5 to visit 6.

Inclusions:

- All ARIC participants with data on physical function and other necessary covariates at visit 5

Exclusions:

- Race other than black and white
- Missing data on physical function and other covariates at visit 5
- Missing data on physical function at visit 6 for longitudinal analyses

Exposure: Clinically recognized varicose veins

- We will capture all ARIC participants who had diagnosis of varicose veins after visit 1 through visit 5.
- Varicose veins will be defined by relevant diagnosis during hospitalization or outpatient visits.
  - Hospitalization due to varicose veins will be identified from ARIC hospitalization data and CMS Medicare data (ICD-9 codes: 454.xx).
  - Outpatient visits for varicose veins will be identified from CMS Medicare data (ICD-9 codes: 454.xx) (at least two visits for varicose veins as primary exposure and at least a visit as secondary exposure)

Outcomes:

1. **Physical Function**
   a. The Short Physical Performance Battery (SPPB)
      - SPPB includes three components of physical performance such as gait speed (i.e., time to walk 4 meters), chair stands (i.e., time to complete 5 chair stands), and standing balance (i.e., semi tandem stand, side-by-side stand, tandem stand).
      - The SPPB summary score was calculated by summing the scores (0-4 for each measures) from the three components, ranging from 0 (poorest) to 12 (best), and SPPB score ≤6 or ≤9 will be considered as poor physical function.[13, 14] We will also consider each component of gait speed, chair stands, and standing balance, separately. ≤2 or ≤3 points of each of three components will be considered as poor physical function.[13]
      - We will also calculate walking velocity (m/sec), dividing 4 meter by the time (sec) to complete 4 meters walk, use it as a continuous variable.
   b. Grip strength
      - We will consider grip strength in kilograms of force using a dynamometer and the better of two trials will be used for our analysis.
      - Grip strength (kg) ≤median value will be considered as poor grip strength.

2. **Physical activity**
   Physical activity in ARIC was assessed via a modified interviewer-administered Baecke Questionnaire. We will consider sport during leisure time and leisure time (excluding sport) activities, and current American Heart Association (AHA) physical activity guidelines. Participants itemized leisure time exercise activities and answered questions regarding the frequency of participation in each, hours per week and months per year performing each activity. Each activity is converted into a metabolic equivalent of task (MET) based on its intensity, as per the compendium of Physical Activities.[15]
   a. AHA physical activity guideline[16]
      - Physical activity levels were categorized into ideal, intermediate and poor.
      - Ideal: ≥75 min/week of vigorous intensity (>6 METs) or >150 min/week of moderate (3-6 METs), or ≥150 min/week of any combination of moderate + vigorous intensity exercise

- Intermediate: 1-74 min/week of vigorous intensity or 1-149 min/week of moderate, or 1-149 min/week of any combination of moderate + vigorous intensity exercise
- Poor: 0 min/week of moderate or vigorous exercises

b. Sport activity
- We will consider the score of sport activity and total volume of activity during leisure time.
- The score of sport activity was expressed as the average of the four items one to five-point score. The four items included participants itemized sport activities and questions regarding the frequency of participation in each, hours per week and months per year performing each activity.
- Total volume of activity (a continuous variable of MET*min/week) will be expressed as a multiplicative combination of intensity, duration and frequency of sport activity.
- The score of sport activity and total volume of activity ≤median values will be considered as poor sport activity.

c. Leisure time activity
- We will consider score of leisure time activity.
- The score of leisure time activity was expressed as the average of the three items one to five-point score. The three items included frequency of watching television, walking, and bicycling.
- The score of leisure time activity ≤median values will be considered as poor leisure time activity.

3. Frailty

Participants will be categorized into three groups: frailty (if ≥3 of the listed components were present), pre-frailty (if 1-2 of the listed components were present) and non-frailty (if none of the listed components were present) as done previously.[17]

Table. Frailty definition of each component

Components	**Definition**
Weight loss	Unintentional weight loss of 10% between visit 4 and visit 5 or body mass index (BMI) <18.5kg/m^2
Slowness	The 20th percentile in sex- and height-adjusted gait speed during a 4-m walk test using the cutoff values established from CHS[18]
Exhaustion	Responded "some of the time" or "most of the time" to 2 questions of the following the 11-item Center for Epidemiologic Studies-Depression scale (CESD) questions: "I felt everything I did was an effort" or "I could not get going"
Weakness	The 20th percentile in sex- and BMI-specific grip strength using the cutoff values established from CHS[18]
Low physical activity	The 20th percentile in sex-specific Baecke leisure sport activity index

Covariates: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of cardiovascular disease (coronary heart disease,

stroke or heart failure), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, reported history of diabetes, or use of anti-diabetes medication), lipid parameters (Total cholesterol, HDL cholesterol and LDL cholesterol), antidyslipidemia medications, ankle brachial index (ABI), and health insurance status at visit 5.

Statistical Analysis:

1. We will summarize baseline characteristics by absence and presence of varicose veins.
2. Subsequently, we will quantify the cross-sectional association of varicose veins with physical function, physical activity, and frailty as continuous and/or dichotomous outcome variables using linear and logistic regression models, as appropriate.
    - Linear regression models: the scores of physical function (the scores of SPPB, gait speed, chair stands, standing balance, and grip strength [kg]), physical activity (the score of sport and leisure time, and MET-min/week), the score of frailty (the score of composite and individual weight loss, exhaustion, low physical activity, slowness, and weakness)
    - Logistic regression models: SPPB (≤6 vs. >6), gait speed (≤2 vs. >2), chair stands (≤2 vs. >2), standing balance (≤2 vs. >2), grip strength (≤ median value vs. >median value), sport and leisure time activities (≤ median value vs. >median value), AHA recommendation physical activity (poor vs. ideal or intermediate) and frailty (frailty vs. none or pre-frailty). We will repeat the analysis using 9 for overall score and 3 for individual component score as thresholds.
    - Several models will be constructed to evaluate the impact of potential confounders.
      Model 1: Crude
      Model 2: adjusted for demographic variables (age, gender, race, and education levels)
      Model 3: Model 2 + body mass index, hypertension, diabetes, total cholesterol, HDL-cholesterol, antidyslipidemia medications, history of cardiovascular disease, smoking status, alcohol intake and ABI (the lowest values of both legs)
3. We will evaluate the association between history of varicose veins at visit 5 and subsequent changes in physical function, physical activity and frailty as continuous and/or dichotomous outcome variables in longitudinal data from visit 5 and 6 using mixed effect models and logistic regression models, as appropriate.
    - Mixed-effect model: changes in physical function (e.g., walking velocity [m/sec]) and physical activity (e.g., MET-min/week) from visit 5 to 6
    - Logistic regression models: Incident of low physical function and physical activity, and incident of frailty at visit 6 (SPPB [≤6 vs. >6], gait speed [≤2 vs. >2], chair stands [≤2 vs. >2], standing balance [≤2 vs. >2], grip strength [≤ median value vs. >median value], sport and leisure time activities [≤ median value vs. >median value], AHA recommendation physical activity [poor vs. ideal or intermediate] and frailty [frailty vs. none or pre-frailty]). We will repeat the analysis using 9 for overall score and 3 for individual component score as thresholds.
    - Several models will be constructed to evaluate the impact of potential confounders as above.
4. We will conduct a few sensitivity analyses.
    - To compare the contributions of varicose veins to physical function, physical activity, and frailty in subgroups, we will perform subgroup analysis according to

age, gender, race, hypertension, diabetes, history of cardiovascular disease, smoking status and insurance status (e.g., Medicare advantage plan).

- To account for potential bias due to population attrition, we will repeat our analyses using inverse propensity score for attrition weight (IPAW) methods.[19] We will estimate the marginal and conditional probability of remaining in the study to generate base and stabilized weights using data prior to visit 5 (mainly visit 4 data and most recent annual/semiannual follow-up telephone call and hospitalization data).[20]

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 __ X _ No
(This file ICTDER 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 ____ 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/mantrack/maintain/search/dtSearch.html

__ **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)?
#MP 2312: Ankle-brachial index and physical function and activity in older individuals: the Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References

1. Hamdan A. Management of varicose veins and venous insufficiency. *JAMA*. 2012;308:2612-21.
2. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, Lohr JM, McLafferty RB, Meissner MH, Murad MH, Padberg FT, Pappas PJ, Passman MA, Raffetto JD, Vasquez MA, Wakefield TW, Society for Vascular S and American Venous F. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53:2S-48S.
3. Chang SL, Huang YL, Lee MC, Hu S, Hsiao YC, Chang SW, Chang CJ and Chen PC. Association of Varicose Veins With Incident Venous Thromboembolism and Peripheral Artery Disease. *JAMA*. 2018;319:807-817.
4. Engbers MJ, Karasu A, Blom JW, Cushman M, Rosendaal FR and van Hylckama Vlieg A. Clinical features of venous insufficiency and the risk of venous thrombosis in older people. *Br J Haematol*. 2015;171:417-23.
5. Muller-Buhl U, Leutgeb R, Engeser P, Achankeng EN, Szecsenyi J and Laux G. Varicose veins are a risk factor for deep venous thrombosis in general practice patients. *VASA*. 2012;41:360-5.
6. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR and Eklof B. Chronic venous disease. *N Engl J Med*. 2006;355:488-98.
7. Wrona M, Jockel KH, Pannier F, Bock E, Hoffmann B and Rabe E. Association of Venous Disorders with Leg Symptoms: Results from the Bonn Vein Study 1. *Eur J Vasc Endovasc Surg*. 2015;50:360-7.
8. Beebe-Dimmer JL, Pfeifer JR, Engle JS and Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol*. 2005;15:175-84.
9. van Uden CJ, van der Vleuten CJ, Kooloos JG, Haenen JH and Wollersheim H. Gait and calf muscle endurance in patients with chronic venous insufficiency. *Clin Rehabil*. 2005;19:339-44.

10. de Moura RM, Gomes Hde A, da Silva SL, Britto RR and Dias RC. Analysis of the physical and functional parameters of older adults with chronic venous disease. *Arch Gerontol Geriatr*. 2012;55:696-701.
11. Cetin C, Serbest MO, Ercan S, Yavuz T and Erdogan A. An evaluation of the lower extremity muscle strength of patients with chronic venous insufficiency. *Phlebology*. 2016;31:203-8.
12. Clarke-Moloney M, Godfrey A, O'Connor V, Meagher H, Burke PE, Kavanagh EG, Grace PA and Lyons GM. Mobility in patients with venous leg ulceration. *Eur J Vasc Endovasc Surg*. 2007;33:488-93.
13. Matsushita K, Ballew SH, Sang Y, Kalbaugh C, Loehr LR, Hirsch AT, Tanaka H, Heiss G, Windham BG, Selvin E and Coresh J. Ankle-brachial index and physical function in older individuals: The Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis*. 2017;257:208-215.
14. Windham BG, Harrison KL, Lirette ST, Lutsey PL, Pompeii LA, Gabriel KP, Koton S, Steffen LM, Griswold ME and Mosley TH, Jr. Relationship Between Midlife Cardiovascular Health and Late-Life Physical Performance: The ARIC Study. *J Am Geriatr Soc*. 2017;65:1012-1018.
15. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC and Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43:1575-81.
16. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Jr., Svetkey LP, Wadden TA, Yanovski SZ, Kendall KA, Morgan LC, Trisolini MG, Velasco G, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76-99.
17. Kucharska-Newton AM, Palta P, Burgard S, Griswold ME, Lund JL, Capistrant BD, Kritchevsky SB, Bandeen-Roche K and Windham BG. Operationalizing Frailty in the Atherosclerosis Risk in Communities Study Cohort. *J Gerontol A Biol Sci Med Sci*. 2017;72:382-388.
18. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA and Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-56.
19. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, Evans DA and Mendes de Leon CF. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology*. 2012;23:119-28.
20. Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, Coker LH, Coresh J, Couper DJ, Griswold ME, Heiss G, Knopman DS, Patel MD, Penman AD, Power MC, Selnes OA, Schneider AL, Wagenknecht LE, Windham BG, Wruck LM and Mosley TH. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study. *Am J Epidemiol*. 2014;179:956-66.