ARIC Manuscript Proposal # 3244

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

1.a. Full Title: Peripheral artery disease and its association with use of cigars, pipes and smokeless tobacco in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **PAD and tobacco exposure**

2. Writing Group:
Writing group members: Jeremy R. Van't Hof, Wendy Wang, Kunihiro Matsushita, Aaron R. Folsom, Pamela L. Lutsey

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

First author: **Jeremy Van't Hof**
    Address: 420 Delaware St SE
          Minneapolis, MN 55455

          Phone: (507) 227-4445   Fax:
          E-mail: vanth008@umn.edu

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).
    Name: **Pamela L Lutsey**
    Address: 1300 South 2nd St, Suite 300
          Minneapolis, MN 55126

          Phone: (612) 624-5812   Fax: (612) 624-0315
          E-mail: Lutsey@umn.edu

3. Timeline:
Data analysis will begin immediately. Manuscript preparation will be performed over the next 6 months. Abstract will be submitted in October for the 2019 Epi and Lifestyle Meeting

4. Rationale:
Peripheral artery disease (PAD) is a common, atherosclerotic disease affecting over 200 million people worldwide.[1] PAD is associated with high rates of mortality and comorbid cardiovascular disease (CVD).[2,3] Adverse limb events, including amputation and leg revascularization, are also common.[2,3] People with symptomatic PAD are limited in their exercise capacity and experience a

reduced quality of life compared to those without the disease.[4,5] Many observational studies have demonstrated the association between smoking and PAD. A 2014 meta-analysis of 68 studies reported a hazard ratio of 2.7 (95% CI 2.28-3.21) for incident PAD for current smokers compared to nonsmokers.[6] This positions smoking as the strongest modifiable risk factor for developing PAD,[7,8] and makes it more impactful in the development of PAD than other cardiovascular diseases.[9] Currently, ARIC data are being used to better understand the risk of incident PAD due to smoking.

Data on the association of smoking and PAD is largely limited to cigarette use which has declined among adults in the United States over the past 50 years.[10] However, in the last decade, the sales of other forms of tobacco, including cigars, loose tobacco for pipes or roll your own cigarettes, and smokeless tobacco, have increased and self-reported use has remained unchanged or increased.[11] This trend is particularly worrisome due to a higher percentage of use in the young adult population. The National Survey on Drug Use and Health evaluates tobacco use in the 30 days prior to the survey. In 2016, of young adults ages 18-25 years, 8.8% reported current cigar use, 1.7% were pipe smokers and 5.2% used smokeless tobacco.[12] There are limited data evaluating the association of cigars, pipes and smokeless tobacco (CPS) with CVD.[13–19] Much of the current understanding of this relationship comes from 2 prospective cohort studies, the Cancer Protection Study I and II which were conducted by the American Cancer Society. These studies enrolled 1.2 million men and women and among other questions, surveyed tobacco use among male participants. Mortality and cause of death due to different exposures were evaluated. Current pipe smokers experienced elevated risk of coronary heart disease (CHD) mortality and stroke mortality, HR 1.30 (95% CI 1.18-1.43) and HR 1.27 (95% CI 1.09-1.48), respectively compared to no tobacco use.[14] Similarly, the exclusive use of smokeless tobacco, most specifically chewing tobacco and/or snuff was associated with increased risk for CVD death. Multivariable adjusted hazard ratios for CHD mortality and stroke mortality were significantly elevated, HR 1.12 (95% CI 1.03-1.21) and HR 1.46 (95% CI 1.31-1.64) respectively when compared to those with no tobacco use history.[13] Cigar smoking was associated with increased CHD mortality but only in those 30-74 years old, HR 1.3 (95% CI 1.05-1.62) compared to never smokers.[15] All referenced analyses of the Cancer Protection Studies excluded current and former cigarette users. Smokeless tobacco use and CVD incidence (defined as CHD or stroke) was analyzed using ARIC data and was shown to have a positive association independent of cigarette use, HR 1.27 (95% CI 1.06-1.52).[17] To our knowledge the association of cigars, pipes and smokeless tobacco with PAD has not been described. Thus, this study seeks to evaluate to the association of cigar, pipe smoking and smokeless tobacco use with incident PAD in participants with and without a history of cigarette smoking.

5.   Main Hypothesis/Study Questions:
The use of cigars, pipes or smokeless tobacco will be associated with greater risk of incident PAD than non-use. The association will be more pronounced among never and former cigarette smokers than among current cigarette smokers.

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).

<u>Study design</u>: prospective cohort study from baseline survey to most recent follow up

<u>Inclusion/Exclusion</u>:
We will exclude participants with prevalent PAD and intermittent claudication, as well as those whose race was other than black or white. Participants will be excluded if they have missing data for tobacco use or ankle brachial index at baseline.

<u>Variables</u>
   <u>Exposures</u>:
      1) Current vs former or never users of cigars or pipes.*
      2) Current vs former or never users of smokeless tobacco.*

      *Use of cigars, pipes and smokeless tobacco was also queried at visits 1, 2, 3 and 4. We will update exposure status through visit 4, by modeling exposures as time-dependent variables.

   <u>Primary outcome</u>: Incident PAD: Specifically, PAD-related hospitalizations will be identified via ICD codes, according to the definition currently being used in ARIC.

   <u>Possible effect modifiers or mediators</u>: Sex, race, diabetes, hypertension, systolic blood pressure, antihypertensive medication use.

   <u>Other confounders/covariates</u>: Age, race, sex, ARIC field center, CVD history, diabetes, LDL cholesterol, statin use, kidney function, BMI, alcohol intake, leisure activity level, income, education, cigarette smoking status.

<u>Statistical analysis</u>
   - Baseline characteristics of participants will be described using means and proportions stratified by exposure to cigars, pipe smoking or smokeless tobacco
   - PAD incidence will be calculated, stratified by cigarette smoking
   - Cox proportional hazards regression will be used to evaluate the relationship between the use of cigars, pipes and smokeless tobacco and incident PAD. The primary exposures will be modeled as time-dependent variables, updating exposure status from visit 1 through visit 4. For the primary analyses we will adjusting for cigarette smoking status (as has been done previously in ARIC when evaluating smokeless tobacco use[17]).
      o Model 1 will adjust for age, sex, race and ARIC site (5-level race-site variable), cigarette smoking status (current, former, never).
      o Model 2 will adjust for model 1 plus BMI, alcohol intake, leisure activity level, income and education.
      o Model 3 will further adjust for CVD history, SPB, antihypertensive use, diabetes, LDL cholesterol, cholesterol lowering medication use, kidney function.
   - Interactions by race, sex, hypertension status, and diabetes status will evaluated, using cross-product terms. Additionally, given inherent interest, stratified results will be presented.
   - Sensitivity analyses will be conducted stratifying by baseline cigarette use (current, former, never). If precision is poor, the former and never groups may be combined.

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 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   __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/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)?**

#1832: Risk prediction model for incident PAD in the ARIC cohort (Matsushita, Kalbaugh)
#1575: Risks of incident cardiovascular disease among users of smokeless tobacco in
the ARIC study (Yatsuya, Folsom)
#2940: Smoking, its cessation, and future risk of peripheral artery
disease (Ding, Matsushita)
#1638: Burden of smoking-related morbidity and mortality and benefits associated with smoking
cessation in a middle-aged US population: The Atherosclerosis Risk in Communities Study
(Huxley, Folsom)

**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. 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.

Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Center for Behavioral Health Statistics and Quality (CBHSQ), Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (HHS), and by RTI International, a trade name of Research Triangle Institute, Research Triangle Park, North Carolina. **Table 7.31B – Tobacco Product and Alcohol Use in the Past Month among Persons Aged 18 to 25, by Gender: Percentages, 2002-2013. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2013/NSDUH-DetTabs2013.htm#tab7.30b**

References:
1.   Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UKA, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *Lancet*. 2013;382:1329-1340. http://www.ncbi.nlm.nih.gov/pubmed/23915883.
2.   Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, Darius H, Burghaus I, Trampisch HJ, German Epidemiological Trial on Ankle Brachial Index Study Group. Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease. *Circulation*. 2009;120:2053-2061. http://www.ncbi.nlm.nih.gov/pubmed/19901192.
3.   Van't Hof JR, Bonaca MP, Weinhandl E, Oldenburg N, Chase M, Beckman JA. Incidence Of Major Adverse Cardiovascular And Limb Events In Medicare Patients With Peripheral Artery Disease. *J Am Coll Cardiol*. 2018;71:A2080. https://linkinghub.elsevier.com/retrieve/pii/S0735109718326214.
4.   McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The Ankle Brachial Index Is Associated with Leg Function and Physical Activity: The Walking and Leg Circulation

Study. *Ann Intern Med*. 2002;136:873. http://annals.org/article.aspx?doi=10.7326/0003-4819-136-12-200206180-00008. Accessed September 3, 2018.

5. Dumville JC, Lee AJ, Smith FB, Fowkes FGR. The health-related quality of life of people with peripheral arterial disease in the community: the Edinburgh Artery Study. *Br J Gen Pract*. 2004;54:826-831. http://www.ncbi.nlm.nih.gov/pubmed/15527608. Accessed September 3, 2018.

6. Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. *Heart*. 2014;100:414-423. http://www.ncbi.nlm.nih.gov/pubmed/23922053.

7. Selvin E. Prevalence of and Risk Factors for Peripheral Arterial Disease in the United States: Results From the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738-743. http://circ.ahajournals.org/cgi/doi/10.1161/01.CIR.0000137913.26087.F0. Accessed September 4, 2018.

8. Benjamin EJ, Virani SS, Callaway CW, … Muntner P. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137:CIR.0000000000000558. http://www.ncbi.nlm.nih.gov/pubmed/29386200.

9. Price J, Mowbray PI, Lee AJ, Rumley A, Lowe GDO, Fowkes FGR. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease; Edinburgh Artery Study Edinburgh Artery Study. *Eur Heart J*. 1999;20:344-353. https://academic.oup.com/eurheartj/article-lookup/doi/10.1053/euhj.1998.1194. Accessed September 4, 2018.

10. Cigarettes: The Rise and Decline But Not Demise of the Greatest Behavioral Health Disaster of the 20th Century | Agency for Healthcare Research & Quality. Content last reviewed July 2015. https://www.ahrq.gov/professionals/education/curriculum-tools/population-health/abrams.html.

11. Agaku IT, Alpert HR. Trends in annual sales and current use of cigarettes, cigars, roll-your-own tobacco, pipes, and smokeless tobacco among US adults, 2002–2012. *Tob Control*. 2016;25:451-457. http://www.ncbi.nlm.nih.gov/pubmed/25899447.

12. Ahrnsbrak R, Bose J, Hedden SL, Lipari RN, Park-Lee E, Tice P. *National Survey on Drug Use and Health Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health Results from the 2016 National Survey on Drug Use and Health*.; 2016. https://www. Accessed September 4, 2018.

13. Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control*. 2005;16:347-358. https://link.springer.com/content/pdf/10.1007%2Fs10552-004-5519-6.pdf.

14. Henley SJ, Thun MJ, Chao A, Calle EE. Association Between Exclusive Pipe Smoking and Mortality From Cancer and Other Diseases. *JNCI J Natl Cancer Inst*. 2004;96:853-861. https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djh144. Accessed August 31, 2018.

15. Jacobs EJ, Thun MJ, Apicella LF. Cigar smoking and death from coronary heart disease in a prospective study of US men. *Arch Intern Med*. 1999;159:2413-2418. http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.159.20.2413. Accessed August 31, 2018.

16. Iribarren C, Tekawa IS, Sidney S, Friedman GD. Effect of Cigar Smoking on the Risk of Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, and Cancer in Men. *N Engl J Med*. 1999;340:1773-1780. http://www.nejm.org/doi/abs/10.1056/NEJM199906103402301. Accessed August 31, 2018.

17. Yatsuya H, Folsom AR, ARIC Investigators for the A. Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. 2010;172:600-605. http://www.ncbi.nlm.nih.gov/pubmed/20688904. Accessed August 30, 2018.

18. Carstensen JM, Pershagen G, Eklund G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. *J Epidemiol Community Health*. 1987;41:166-172. http://www.ncbi.nlm.nih.gov/pubmed/3655638. Accessed August 31, 2018.

19. Shaper AG, Wannamethee SG, Walker M. Pipe and cigar smoking and major cardiovascular events, cancer incidence and all-cause mortality in middle-aged British men. *Int J Epidemiol*. 2003;32:802-808. http://www.ncbi.nlm.nih.gov/pubmed/14559754. Accessed August 31, 2018.

20. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol*. 2007;18:629-636. http://www.ncbi.nlm.nih.gov/pubmed/17215445.