1.a. **Full Title**: Lung function and risk of peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: lung function and PAD

2. **Writing Group**:
   Writing group members: Ning Ding, Maya Salameh, Elizabeth Selvin, Naresh M. Punjabi, Gerardo Heiss, Kunihiro Matsushita; others welcome

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

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3. **Timeline**: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. **Rationale**:  
Lung function is typically assessed as forced vital capacity (FVC), forced expiratory volume during first second duration (FEV1) and their ratio (FVC/FEV1) using standardized spirometry. Studies have reported that impaired lung function increases the risk of cardiovascular
diseases, including coronary heart disease [1, 2], stroke [3], atrial fibrillation [4], and heart failure [5]. However, the association between lung function and peripheral artery disease (PAD) is less well characterized. Only a few, primarily cross-sectional, studies have investigated the association between pulmonary diseases (e.g., chronic obstructive pulmonary disease [COPD], asthma) and PAD, and the results have been inconsistent [6-8].

There are several pathophysiological mechanisms that could link impaired lung function to the risk of PAD. Chronic airway inflammation in COPD and asthma can contribute to a systematic inflammatory response, which plays a critical role in the pathogenesis of atherosclerosis [9, 10]. Hypoxia due to impaired lung function might contribute to walking-induced muscle pain, which is the typical symptom for PAD, and delayed wound healing in patients with severe PAD, namely critical limb ischemia (CLI). Other pathological processes such as systemic endothelial dysfunction, oxidative stress, impaired vascular reactivity, and platelet activation may constitute a link between these two conditions [11-13].

Therefore, to comprehensively quantify the association of lung function with incident PAD and CLI, we will study longitudinal data in the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:
Hypothesis: Reduced lung function is associated with the risk of incident PAD.

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).

Inclusions:
- All white and black ARIC participants at visit 1 who provided relevant data on lung function variables of interest, did not have a history of PAD, and had outcome information during follow-up.

Exclusions:
- Ethnicity other than black or white
- Missing relevant data on lung function variables of interest
- Preexisting PAD at baseline defined as ankle-brachial index ≤0.9, self-reported intermittent claudication based on Rose questionnaire, or self-reported history of peripheral revascularization
- Missing data on relevant baseline covariates or PAD outcomes during follow-up

Exposures (independent variables):
Lung function will be our primary exposure, but we will also explore the history of pulmonary diseases.
- Lung function at V1: assessed using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical Inc) and Pulmo-Screen II software (PDS Healthcare Products Inc). At least 3 acceptable spirograms were obtained from a minimum of 5 forced expirations [14].
  - Percent-predicted FVC: the maximal volume of gas exhaled after maximal inspiratory effort expressed as a percentage of the predicted value based on age, sex, height, and
race according to recommendations from the Epidemiology Standardization Project [15].

- FEV1/FVC: the proportion of gas exhaled in the first second of expiration out of FVC.
- Lung function pattern [14]:
  - normal (percent-predicted FVC ≥ 80% and FEV1/FVC ≥ 70%)
  - obstructive (percent-predicted FVC ≥ 80% and FEV1/FVC < 70%)
  - restrictive (percent-predicted FVC < 80% and FEV1/FVC ≥ 70%)
  - mixed (percent-predicted FVC < 80% and FEV1/FVC < 70%)

Self-reported pulmonary diseases at V1: history of pulmonary disease was obtained via a standardized questionnaire by trained personnel. Participants were also asked whether they were ever diagnosed with bronchitis/emphysema/asthma, and whether these were confirmed by a doctor. Chronic bronchitis was defined as productive cough for at least 3 months in two contiguous years. COPD was defined by a positive response to a physician diagnosis of either emphysema or chronic bronchitis.

Outcomes (dependent variables):
- PAD and CLI: PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature [16, 17]: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); peripheral vascular disease, unspecified (443.9); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 will be considered CLI. Also, we will consider any cases with the above code as CLI when the following codes coexist: leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4).

Covariates:
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, systolic blood pressure, diastolic blood pressure
- Lifestyle: smoking status (current, former, never), pack-years of smoking, alcohol habit
- Comorbidities: obesity, dyslipidemia, diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, kidney function, C-reactive protein, history of CHD and stroke

Statistical Analysis:
- We will use Cox proportional hazards regression models to quantify the association of lung function and self-reported pulmonary diseases with incident PAD/CLI.
- Percent-predicted FVC and FEV1/FVC will be analyzed as continuous variables and into quartiles.
- We will construct 2 models. Model 1 will adjust for sociodemographics characteristics. Model 2 will further adjust for cardiovascular risk factors listed above.
- We will use likelihood ratio test to test for interaction by key demographic and clinical factors (e.g., age, sex, race, smoking, alcohol use and diabetes).
- Given the potential impact of the competing risk of death for estimating PAD risk, we will run Fine and Gray’s proportional subhazards models.
- The data will be analyzed in Stata 14.

**Limitations:**
- The definition of PAD (and CLI) relied on hospital discharge diagnostic codes, thus asymptomatic cases or mild cases were unlikely to be captured.
- We will not be able to eliminate the possibility of residual confounding as is the case in any observation study.
- ARIC predominantly included whites and blacks, so the results may not be generalizable to races other than whites and blacks.

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/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)?

    # 1377 Relationship between pulmonary disease, lung function and incident hospitalized heart failure: The Atherosclerosis risk in communities (ARIC) study
    # 2688 Lung function and subsequent risk of chronic kidney disease: 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? __X__ Yes    ____ No

11.b. If yes, is the proposal
   ___  A. primarily the result of an ancillary study (list number* 2014.05________)
   ___  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.cscu.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. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

Reference


