1.a. Full Title:

Admixture mapping analysis of peripheral arterial disease (PAD) and ankle brachial index (ABI): The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): admixture map of PAD and ABI

2. Writing Group:

Writing group members:


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

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3. **Timeline:**
   - Starting Analyses: October 2008
   - First Draft: February 2008
   - Submission for Publication: April 2008

4. **Rationale:**

   Approximately 8 million Americans have peripheral arterial disease (PAD), which affects 12-20% of those aged 65 or older\(^1\). Classic risk factors for PAD include age, race/ethnicity, smoking, diabetes, cholesterol, hypertension, chronic kidney disease, and the presence of other atherosclerotic cardiovascular disease\(^2\text{-}^4\). As well, newer biomarker risk factors have also been found to predict PAD incidence\(^5\text{-}^9\). However, none of these risk factors, traditional or novel, fully accounts for the difference in risk between African-Americans and Caucasians. In general, African-Americans have approximately twice the risk of PAD compared to Caucasians even when the contribution of other known risk factors is considered. Genetic variants are hypothesized to at least partially explain this difference.

   Admixture mapping is a technique that takes advantage of the long-range linkage disequilibrium (LD) between ancestry informative markers (AIMs) in recently admixed populations such as African-Americans\(^10\text{-}^11\). (AIMs are markers with large allele frequency differences between populations.) The mixing of populations creates large areas of the genome which are identifiably inherited from one of the specific ancestral groups of the mixing populations. This type of LD has been termed admixture LD\(^12\). Admixture mapping capitalizes on the resulting admixture LD or ancestry informativeness of a genomic region to find genetic variants that underlie differences in disease risk between the two ancestral groups, i.e. Caucasian and African\(^10\text{-}^11\). If significant genetic variants are in admixture LD with PAD and/or ABI risk alleles, then we can identify directly which alleles/variants may be responsible for the difference in risk between Caucasians and African-Americans. Given the relatively recent admixture of Africans and Caucasians and the striking difference in PAD risk between African-Americans and Caucasians, admixture mapping is an approach well suited to this problem.

5. **Main Hypothesis/Study Questions:**

   Ancestral background (i.e., proportion/percent European ancestry) will be associated with PAD and ABI outcomes. Since PAD and ABI prevalence differ by race/ethnicity, we also hypothesize that individuals with African-American ancestry will be identified to contain loci underlying these differences in disease risk in a specific area of the genome that are in admixture LD with PAD and/or ABI risk alleles.
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).

**Inclusion/Exclusion:** African-Americans who: 1) gave consent for DNA use by for-profit investigators, 2) have ancestry informative markers (AIMs) data available, and 3) either Jackson or Forsyth County

**Outcomes:**
1) ABI continuous at Visit 1, dropping those with ABI > 1.3
3) ABI at Visit 1 with ABI > 0.90 as cases and ≤0.90 as controls (still dropping those ABI > 1.3 first)

Since there are only ~210 PAD cases in African-Americans in ARIC at baseline, we may also consider using ABI of 1.0 as a cut point, or using the bottom 20% and middle 20% of the ABI distribution as “cases” and “controls”, respectively. (ABI has a different distribution from other continuous variables, with those at both the highest and lowest ends at risk, thus the middle 20% would need to be controls.)

**Exposure:** 1536 ancestry informative markers/percent European ancestry

*Possible* covariates include, but are not limited to, age, sex, socio-economic status, adiposity (BMI and waist circumference), lipid levels, diabetes, fasting glucose, hypertension, blood pressure, medication use (anti-hypertensives, statins), smoking status, and physical activity

**Analysis Plan:**

First, proportion European ancestry will be calculated and associations with PAD and ABI will be evaluated using staged models to assess potential confounding effects. Logistic regression will be used for PAD yes/no and linear regression will be used for ABI. If the ABI frequency distribution is skewed, we will natural log transform these data. To assess the appropriate functional form of proportion European ancestry with PAD and ABI, we will use generalized additive models (GAMs) with a cubic B-spline function to construct splines. GAMs extend the generalized linear model by allowing fit of nonparametric function to estimate the associations of predictors and outcomes. To search for genetic variants associated with PAD and/or ABI, we will use an admixture mapping approach. ANCESTRYMAP software, which employs a Bayesian Markov Chain Monte Carlo method, will be used for both the calculation of proportion European ancestry and admixture mapping. Ancestral population data from HapMapYoruban and CEPH families will be used for the Bayesian prior distribution for reference and variant alleles.

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

__X__ 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?

__X__ 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”?

__X__ 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?

__X__ 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)?

Linda Kao has a proposal for admixture mapping of CVD and related metabolic traits (#1309). However, we have confirmed with her that no one else is interested in PAD and ABI admixture hypothesis, and have also invited members of her group to participate in our manuscript.

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

__X__ A. primarily the result of an ancillary study (list number* _2004.10_)  
____ 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/](http://www.cscu.unc.edu/aric/forms/)

12. 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.
References:


