1.a. Full Title: Risk of cardiovascular event in relation to age at natural menopause (ANM) associated genetic variants

b. Abbreviated Title (Length 26 characters):

Cardiovascular risk & ANM SNPs

2. Writing Group:

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

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3. **Timeline:**

Analyses are already done in the Framingham Heart Study. We are expecting to combine these results with ARIC results mid-July. A paper draft will be ready this summer.

4. **Rationale:**

Early menopause (defined by menopause occurring before 45 years of age) is associated with an increased risk of cardiovascular diseases. Genome-wide association studies identified 56 independent SNPs associated with age-at-natural menopause (ANM). It is unknown whether the genetic predisposition to earlier menopause also increases the risk of cardiovascular disease, or whether the increased risk in women with earlier menopause is due to non-genetic factors. If the genetic predisposition to earlier ANM also increases cardiovascular disease risk, then it will be important to understand whether this risk is shared by men carrying ANM-lowering alleles as well.

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

We sought to determine the time to the first cardiovascular event in relation to a genetic risk score (GRS) comprising the ANM decreasing 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).**

An independent set of associated SNPs will be obtained from the ANM meta-analysis (Day et al, Nature Genetics, 2015). The selection of SNPs will be done based on genome-wide associated SNPs. This set will be extracted from Haplotype Reference Consortium or 1000 Genomes imputed data.

GRS will be computed using OR-weighted score method that uses the effect sizes of the SNPs from the meta-analysis to compute weights.

We will study time-to-first-cardiovascular events. The outcomes will be: 1) different types of cardiovascular events analyzed separately or 2) a composite end point of cardiovascular events (myocardial infarction, stroke, CHF and death from coronary heart disease).

Association between GRS and time-to-first-cardiovascular-event will be evaluated using Cox proportional-hazards model. The entry point in the Cox model will be age when DNA was drawn also called age at baseline (look for an increased risk of cardiovascular events across the full adult age spectrum).
Analyses will be adjusted on age at baseline, sex, PCs, known cardiovascular risk factors measured at baseline (Body Mass Index, Total cholesterol, Hypertension, Current smoking, Type 2 Diabetes, Lipid treatment) and family relatedness.

The primary analysis will be performed in a sample free of cardiovascular disease (CVD) at baseline with all the covariates included in the model. This analysis will be performed in: 1) all individuals with a GRSxssex interaction term, 2) males only and 3) females only.

Sub-analyses will include:
1) same analysis adjusted only on sex and age at baseline (without PCs & known cardiovascular risk factors),
2) same analysis with GRS divided in two sub-scores (GRS₁ = SNPs belonging to DNA repair pathway and GRS₂ = other SNPs),
3) same analysis with age at natural menopause as the entry date in the Cox model (restriction of the analyses to post-menopausal women only and adjusted on age at natural menopause).

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 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?  __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

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.cscce.unc.edu/ARIC/search.php

__X__ Yes  _______ No  no other study similar to these
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)? None

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

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 __x__ No.