ARIC Manuscript Proposal #3084

PC Reviewed: 12/12/17    Status: _____    Priority: 2
SC Reviewed: _________    Status: _____    Priority: ____

1.a. Full Title: Accelerated epigenetic aging is associated with a prothrombotic hemostatic factor profile

b. Abbreviated Title (Length 26 characters): Epigenetic aging & hemostasis

2. Writing Group:

This is a consortium manuscript. ARIC summary data will be included in a meta-analysis of 11 studies from the Cohorts for Heart & Aging Research in Genetic Epidemiology (CHARGE) Hemostasis Working Group

Writing group members: Representatives from ARIC:
Jim Pankow
Nick Roetker
Eric Boerwinkle
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JP___ [please confirm with your initials electronically or in writing]

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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:
Address:

Phone:    Fax:
E-mail:
3. **Timeline:** Manuscript will be ready to submit by January 2018

4. **Rationale:**

   Advancing age is often associated with an increased coagulation profile typified by increased plasma concentrations of hemostatic factors such as fibrinogen and FVII, and this age-associated prothrombotic hemostatic profile that may underlie associations between age and cardiovascular disease. Typically, studies of aging are performed by comparing the hemostatic/clinical profiles of patients with their chronological age. Though effective, this approach does not inform on the underlying biological changes linking aging and altered hemostatic profiles. Epigenetic biomarkers of aging are tissue specific and associated with a number of clinical outcomes including: mortality, obesity, cancer, cardiovascular disease, HIV-1 infection, and traumatic stress. These epigenetic aging biomarkers have yet to be associated with hemostatic factors.

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

   This manuscript will test the association between accelerated epigenetic aging and a prothrombotic hemostatic profile.

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).**

   Five hemostatic factors and one measure of clotting time will be examined: fibrinogen, plasminogen activator inhibitor 1 (PAI-1), D-dimer, Factor VII (FVII), von Willebrand Factor (vWF), and activated partial thromboplastic time (aPTT).

   All cohorts assessed DNA methylation via the Illumina 450K array. In order to assess epigenetic aging, an online calculator will be used, [https://dnamage.genetics.ucla.edu/](https://dnamage.genetics.ucla.edu/), which allows for the simultaneous estimation of multiple epigenetic aging measures. Three epigenetic aging measures will be used for this analysis: Age Acceleration Difference (AAD), Extrinsic Epigenetic Age Acceleration Difference (EEAD), and Intrinsic Epigenetic Age Acceleration Difference (IEAD).

   Two models will be used to understand the relationship between epigenetic aging and hemostatic factors. For each model the hemostatic factor is the outcome while the epigenetic aging measure is the predictor. The first model is a “basic” model which adjusted for age, age², and sex. The second (full) model adjusts for the basic model terms plus: body mass index (BMI, kg/m²), physical activity (active vs inactive), and smoking status (current, former, never).

   In ARIC the epigenetic age measures are based on methylation assessed at a different examination (visit 2 or 3) than the hemostatic measures (visit 1). Additional “age difference” terms (linear and quadratic) will be added to the full and basic models, with age difference calculated as the difference between the chronological age at methylation assessment and chronological age when the hemostatic factors were assessed.
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? _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.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)?

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://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.