ARIC Manuscript Proposal #3446

PC Reviewed: 8/13/19 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between White Blood Cell Differential Counts and Risk of Abdominal Aortic Aneurysm

b. Abbreviated Title (Length 26 characters): WBC Differentials and AAA

2. Writing Group:

Writing group members: Weihong Tang, Kripa Poudel, Romil Parikh, Pamela L. Lutsey, Ryan Demmer, James S. Pankow, Aaron R. Folsom; others are welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __WT___ **[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).
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3. Timeline: Finish by September 2019

4. Rationale:

Abdominal aortic aneurysm (AAA) is an important vascular disease in older adults[1] and rupture of AAA is associated with a high mortality rate.[2] The etiology of AAA is complex and not well understood. Among established cardiovascular risk factors, age, male sex, smoking, and increased low-density lipoprotein or total cholesterol increase the risk of AAA.[1, 3] Evidence from animal studies support the role of immune cells, including neutrophils, monocytes/macrophages, and lymphocytes,[4-7] in the pathogenesis of AAA, which is characterized by progressive

degradation and remodeling of extracellular matrix in the aortic wall.[8-10] In ARIC, we identified a strong positive association of clinical AAA incidence with total white blood cell (WBC) counts over a median of 22.5 years of follow-up.[11] This association was independent of other major AAA risk factors. WBC count was also associated with the prevalence of asymptomatic AAA detected by ARIC Visit 5 ultrasound exam.[11] More recently, a UK study of 775,231 participants from an electronic health record database reported a positive association between neutrophil counts at baseline and AAA incidence over a median follow-up of 3.8 years (interquartile range: 1.7 to 6.0 years), independent of eosinophil and lymphocyte counts.[12] They also found a significant and positive, albeit weaker, association between monocyte counts and AAA.[12] The major weakness of this study is the potential influence of reverse causality due to the short follow-up. Another study in the same population focused on low lymphocyte and eosinophil counts as risk factors for 12 cardiovascular diseases and failed to find a significant association for AAA.[13]

5. Main Hypothesis/Study Questions:

We hypothesize that white blood cell differential counts (e.g., neutrophils, monocytes, lymphocytes and eosinophils) measured in middle age will be associated positively with incidence of AAA over the next 20 years.

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).

WBC counts and differential percentages were measured in ARIC at Visit 1 for three of the four field centers (missing for about 86% of participants from Washington county) and at Visit 2 for two field centers (missing Washington county and Jackson). We will calculate counts of each WBC subtype by multiplying total WBC count by the percentage of the corresponding differential. Since neutrophil bands can normally be absent in most individuals, we will replace missing neutrophil bands by zero. Total neutrophil percent will be calculated by adding percentages of segmented neutrophil and band neutrophil. We will exclude individuals with sum of differential percentages less than 95% or greater than 105%.

WBC differential counts derived for Visit 1 will be analyzed as the main exposures. We will apply the following exclusions: 1) WBC or differential counts greater or less than 6 SD from the mean; 2) race other than white or African American; 3) prior AAA surgery or uncertain AAA status during follow-up; 4) missingness for the exposures or important covariates.

We will divide all differentials into 5 categories: below the normal range, three tertiles within the normal range, and above the normal range. We will conduct Cox proportional hazards regression to obtain hazard ratios of incident, clinical AAA associated with the five categories of each differential count in nested multivariate models, with the tertile 1 group within the normal range as the reference group. We will adjust for established risk factors for AAA and other potential confounders (i.e., age, gender, race-center, smoking status, pack-years of smoking, BMI, waist circumference, total cholesterol, HDL cholesterol, triglycerides, use of cholesterol lowering medication, hypertension, peripheral artery disease, diabetes, and prevalent coronary heart

disease at Visit 1) as well as the other differentials (as a continuous variable). We will test for trend in hazard ratios across the four groups (excluding the 'below the normal range' group) using an ordinal variable designating each of the four groups. The proportional hazards assumption will be evaluated by testing for interaction between each differential count exposure and log survival time.

In a secondary analysis, we will analyze the association between the asymptomatic AAA detected at ARIC Visit 5 ultrasound exam and the differential counts that are significantly associated with clinical AAA. We will use logistic regression with weighting for the probability of survival to the Visit 5 exam.

We will also conduct the following sensitivity analysis for clinical AAA: 1) remove AAAs who were diagnosed within 10 years from the baseline; 2) use race-specific cutpoints and also conduct the analysis in whites only to evaluate any residual confounding by race; 3) conduct the analysis separately in ever-smokers and never-smokers reported at baseline visit; 4) analyze the average of differential counts from Visits 1 and 2 as exposures.

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)?
1505. Risk Factors for Abdominal Aortic Aneurysm (Tang)
1505A. Hemostatic Factors and Aortic Aneurysm Incidence (Folsom)

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 (**AS 2009.18: "Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm", R01HL103695, PI Weihong Tang**)**

___ 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.

References:

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