ARIC Manuscript Proposal # 4168

PC Reviewed: 12/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of Leukocyte Telomere Length With Left Atrial Size and Function:

The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): LTL & left atrium

2. Writing Group:
Writing group members: Romil Parikh, Nathan Pankratz, John A. Lane, Dan Arking, Anne Eaton, Lin Yee Chen, Pamela Lutsey, Weihong Tang

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

First author: Romil R. Parikh
Address: Division of Epidemiology & Community Health,
300 West Bank Office Building, 1300 S. 2nd St.,
Minneapolis, MN 55454
Phone: 6128405816
E-mail: parik075@umn.edu

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: Weihong Tang
Address: Division of Epidemiology and Community Health
University of Minnesota
1300 S. 2nd St., Suite 300
Minneapolis, MN 55454
Phone: 612-626-9140
E-mail: tang0097@umn.edu

3. Timeline: 12 months from approval

4. Rationale:

Adverse left atrial (LA) remodeling is a risk factor for stroke and dementia, independent of developing clinical AF.[1-9] LA enlargement indicated by greater LA volume index (LAVI) is a

conventional biomarker of adverse LA remodeling.[1,2] Some evidence indicates that abnormalities in LA function can occur before onset of LA enlargement and are robust predictors for stroke and dementia independent of LA size and left ventricular (LV) structure and function.[4-10] Furthermore, increase in LA size could occur as physiologic adaptation to higher levels of physical activity.[11,12] Recently, we reported that higher cumulative leisure-time physical activity (LTPA) over 24 years was associated with greater LA size, but better LA function independent of LA size.[13] LA size and dysfunction also correlate with age, with a higher prevalence of LA enlargement and dysfunction observed in elderly.[1, 14] Hence, the impact of aging on LA size and function, and its interaction with physical activity needs further clarification.

Telomeres are repetitive, gene-poor regions that cap the ends of DNA and help maintain chromosomal integrity. Coupled to cell division, telomeres lose their nucleotide repeats over time. Telomere shortening is observed throughout the human lifespan including in older adulthood.[32, 3415,16] In addition, stressors within the cellular environment, owing to the cumulative burden of oxidative stress, inflammation, and exposure to vascular risk factors,[8] promote shortening of telomeres, ultimately leading to cellular senescence. Thus, telomere length (TL) in cells including leukocyte telomere length (LTL) is considered a biomarker of ageing.[8] Genetic and environmental factors, such as male gender, elevated BMI, physical inactivity, smoking, alcohol consumption, poor diet, and chronic inflammation, have been associated with shorter LTL.[33, 35, 36, 17-19] Shorter LTL is also associated with cardiovascular disease, adverse left ventricular remodeling, stroke, and dementia.[20-24] However, the association of shorter LTL with LA size and LA function is unclear.

ARIC has obtained estimates for LTL for about 3,353 ARIC participants based on visits 2 or 3 whole genome sequencing (WGS) data from the NHLBI Trans-Omics for Precision Medicine (TOPMed) program.[25] In addition, an R21 study led by Dr. Weihong Tang (1R21AG072530) is expanding the estimates of LTL to the full ARIC cohort using WGS data (visits 1 to 4) from the

NHGRI Centers for Common Disease Genomics (CCDG) programs. In this regard, the ARIC cohort provides a unique opportunity to evaluate midlife measures of LTL with LA size and function measured in late life by 2D speckle tracking echocardiography. We aim to evaluate these associations among White and Black participants in the ARIC cohort.

5. Main Hypothesis/Study Questions:

H1: shorter LTL in midlife will be associated with greater LAVI at visit 5

H2: shorter LTL in midlife will be associated with lower LA function as measured by LA reservoir, conduit, and contractile strain at visit 5, independent of LAVI.

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).

Study Design: Observational population-based study in which independent variable (LTL) was measured in midlife (visits 1-4) and the dependent variables are measured in late-life (visit 5).

Study population:

Inclusion: Black and White ARIC participants who have data on exposure and outcome of interest.

Exclusions: Blacks in Minneapolis center and Washington county center due to small numbers

Exposures/Predictor variables: ARIC has obtained from TOPMed estimation of LTL in a subset of ARIC (n=3,353, 84% visit 2 and 16% visit 3 samples) based on the high pass WGS data (~38X). The R21 study led by Dr. Tang proposed to complete the remaining ARIC estimates using the same methods and the CCDG WGS data,[26] which will yield an approximate 13,000 participants. The ARIC WGS data from TOPMed and CCDG were sequenced by a single lab and

are jointly called by the TOPMed Informatics Research Center to produce a uniform dataset. The TOPMed/CCDG status will also be adjusted for in our data analysis to remove potential confounding. Batch effects will be detected and corrected in the estimates of LTL based on the WGS data.

LTL measure will be split into quintiles (allowing us to assess linearity of associations), considering the highest group as the referent. LTL measure will be inversely normalized. Therefore, there will be no need to do outlier exclusions or standardization.

Outcomes: 2D echocardiographic measures of LA size (LAVI) and function (LA reservoir, conduit and contractile function) measured at Visit 5 (modeled as continuous dependent variables)

Covariates: Age at the time of blood draw, sample visit, whole genome sequencing source (TOPMed vs CCDG), race-center, sex, smoking status (categorical variable, at the time of blood draw), body mass index, total cholesterol, high density lipoprotein cholesterol, use of antihyperlipidemic medications, prevalent diabetes, systolic blood pressure, use of anti-hypertensives, and a composite of prevalent HF, CHD, peripheral artery disease (PAD) or stroke (yes/no). All covariates are measured at time of blood draw. We will conduct sensitivity analyses to evaluate other potential confounders (e.g., WBC count) in the subset of ARIC who have these data.

Statistical analysis

Primary analyses: Serial nested linear regression models will be built as follows:

For LA size: Model 1: unadjusted; Model 2: adjusted for Age at the time of blood draw, sample visit, whole genome sequencing source (TOPMed vs CCDG), race-center, sex; Model 3: fully

adjusted model. For LA function: we will create same models and add LAVI as a covariate in model 3. We will use stabilized inverse probability weighting (sIPW) to account for selection bias due to selection for surviving till and attending V5.

Secondary analyses: We will assess interaction by race and sex by stratification.

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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

_____ 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)?
The most relevant manuscripts include:
MS 3631: Association of leukocyte telomere length with dementia and MCI in the Atherosclerosis Risk in Communities Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ No

11.b. If yes, is the proposal
_x__ A. primarily the result of an ancillary study (Chen, 2015.29; Tang, 2020.25)
___ 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.