ARIC Manuscript Proposal #4386

PC Reviewed: 1/9/24	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Assessing the Contribution of Racial Differences in Elevated Lipoprotein (a) Levels to Disparities in Atherosclerotic Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Lp(a) and ASCVD disparities

2. Writing Group: Jelani K. Grant, Seth S. Martin, Sui Zhang, Kuni Matsushita, Salim S. Virani, Roger S. Blumenthal, Ron Hoogeveen, Eric Boerwinkle, Christie M. Ballantyne, Joe Coresh, Chiadi E. Ndumele; others welcome

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee in <6 months from the date of submission.

4. Rationale:

Racial and ethnic disparities in atherosclerotic cardiovascular disease (ASCVD) exist in the United States (US), with Black men and women having a higher prevalence of ASCVD when compared to their White counterparts.[1] Race is now widely recognized as a social construct, with a growing understanding of the role of social determinants of health (SDoH) in race-based differences of ASCVD outcomes.[2] Prior studies demonstrate that the persistence of racial differences in SDoH, including factors such as income-to-poverty ratio, education, health insurance and food security, underlie the majority of racial disparities in ASCVD events and subsequent cardiovascular and all-cause mortality.[3-5] However, in the US and many other countries, race, ancestry, genetics, and medicine are intertwined in a complex history of structural racism and oppression. While racial/ethnic differences in cardiovascular disease incidence and outcomes are largely due to socioeconomic disparities, race/ethnicity is also associated with genetic ancestry and variants that can confer some biological risk and contribute to health disparities.[6]

One example of a biological factor with genetic underpinnings that may contribute to racial disparities in ASCVD is Lipoprotein (a) [Lp(a)]. Lp(a) is a lipid particle that is causally related to the development of ASCVD, conferring risk through thrombotic, oxidative and inflammatory mechanisms. Lp(a) is predominantly (>90%) determined by genetic variability at the Lp(a) locus.[7] Notably, significant racial/ethnic differences are seen in the distribution and levels of Lp(a), with Black individuals having the highest levels of all ethnic groups, followed by South Asian, White, Hispanic, and East Asian persons.[8 7]

Racial/ethnic differences in Lp(a) can be partly explained by differences in Lp(a) isoform size and single nucleotide polymorphisms (SNPs) within and surrounding the gene locus.[9] Larger isoform size, mediated by the number of “type 2 kringle domains” (KIV-2) repeats, is inversely correlated with plasma Lp(a) levels. Furthermore, a study including participants of the Dallas Heart Study[10] found that Black participants had higher Lp(a) levels compared with White and Hispanic adults for any given isoform size, suggesting that other variables in addition to isoform size may genetically determine Lp(a) levels. In support of the hypothesis that racial differences in cardiovascular disease may in part be explained by genetic variations, a genome-wide association study demonstrated that SNPs in the Lp(a) gene were strongly predictive of the incidence of aortic valve and mitral annular calcification inWhite European, African-American, and Hispanic-American cohorts.[11]

While racial/ethnic differences in Lp(a) are well documented, the contribution of racial/ethnic differences in Lp(a) to ASCVD disparities in the US has not been well characterized in long-term cohort studies. As such, we seek to compare the relative risk associations for ASCVD in association with higher Lp(a) levels between Black and White adults, and to estimate and compare the related population-attributable fraction (PAF) for ASCVD across racial groups.

5. Main Hypothesis/Study Questions:

Aims:

1) To evaluate whether progressively higher Lp(a) levels are similarly associated with higher risk of ASCVD for Black and White adults.
2) To assess whether the percentage of ASCVD events related to elevated Lp(a), as estimated by the population-attributable fraction (PAF), differs for Black and White adults.

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: We will perform a prospective analysis among Black and White participants at ARIC Visit 4 (1996-99) without baseline ASCVD (defined as coronary heart disease or ischemic stroke), evaluating the association of higher Lp(a) with incident ASCVD events occurring after Visit 4. Notably, Visit 4 is the only visit for which Lp(a) has been measured for all participants using the Denka Seiken assay, and is therefore the appropriate baseline for this analysis.

Exposures: The primary exposure will be Lp(a), modeled both categorically and continuously. We will use the clinically utilized cut points of <30 (reference), ≥30 to <50, 50≥ to <100, and ≥100 mg/dL in categorical analysis. In continuous analysis, we will assess risk associated with 10 mg/dL higher Lp(a).

Self-identified Race (White versus Black race) will be assessed as an effect modifier in this analysis. We will stratify analyses by race, and test for statistical interactions between Lp(a) and race on the outcome of ASCVD.

Outcomes: The primary outcome will be incident ASCVD, defined as coronary heart disease (fatal or nonfatal MI, coronary revascularization procedure or CHD death) or ischemic stroke, occurring after Visit 4 through 2020 (or most current follow-up available). The secondary outcomes will be incident coronary heart disease only or incident ischemic stroke only occurring after Visit 4.

Exclusions: Because this analysis is focused upon the association of Lp(a) with incident ASCVD, we will exclude participants with known ASCVD at or prior to Visit 4 (self-reported at Visit 1, or adjudicated events from Visit 1 to Visit 4). We will also exclude participants missing covariates of interest, as well as women taking hormone therapy at baseline that might influence lipid levels.

Covariates: Age, sex, race, education, household income, smoking status, alcohol use, systolic and diastolic blood pressures, blood pressure medication use, LDL-C, triglycerides, diabetes, statin use, and BMI, measured at ARIC Visit 4.

Main Analyses:

1) We will perform univariate comparisons of demographics and clinical characteristics between White and Black adults at Visit 4, using the chi squared test for categorical variables and t tests or Kruskal-Wallis tests for continuous variables. We will also consider comparisons of characteristics across Lp(a) categories, as defined above.
2) We will estimate racial differences in Lp(a), assessing for differences in both median Lp(a) and in the percentages of individuals within each of the Lp(a) categories.
3) We will use multivariable Cox regression models, adjusted for the covariates defined above, to assess the association of higher Lp(a) (defined categorically and continuously) with incident ASCVD and incident CHD. We will create multiplicative interaction terms and perform Likelihood Ratio Tests to assess for effect modification by race of the association between higher Lp(a) and incident ASCVD and CHD events
4) We will estimate the Population Attributable Fraction for ASCVD associated with higher Lp(a) in the overall population, as well as for Black and White adults. Population Attributable Fraction will be estimated using the equation: (P population x (RR-1)) ÷ (P population x (RR-1) + 1), where P will be the prevalence of Lp(a) ≥30 mg/dl and RR is the relative risk. We will consider additional analyses using the PAR to estimate the proportion of the incidence rate difference for ASCVD between White and Black adults that is potentially related to differences in the prevalence of elevated Lp(a).

Limitations:

- There is potential for residual confounding in this observational analysis
- We are only assessing risk associations of Lp(a) at a single time point, however prior studies suggest that there may not be large variation in Lp(a) over time in adult populations
- We do not have information on racial/ethnic groups other than White and Black adults in this analysis

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 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? ____ 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

___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)?

Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W; Atherosclerosis Risk in Communities Study Group. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001 Sep 4;104(10):1108-13.

ARIC Proposal #1610: Associations between lipoprotein(a) levels and cardiovascular outcomes in African Americans: The Atherosclerosis Risk In Communities (ARIC) Study. Writing group members: Christie M. Ballantyne MD, Vijay Nambi MD, Salim S. Virani MD, Ariel Brautbar MD, Ron C. Hoogeveen PhD, Eric Boerwinkle PhD, Gerardo Heiss MD Ph D, A. Richey Sharrett MD DrPH, Josef Coresh MD PhD, Thomas H. Mosley MD, Joel D Morrisett PhD, Aaron R Folsom MD, Diane J. Catellier DrPH.

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

___ A. primarily the result of an ancillary study (list number* _____)
_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __2006.16_____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.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.

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