ARIC Manuscript Proposal Form

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Publication Committee Review Date: **05/13/25**
ARIC Manuscript Proposal Number: **# 4659**

1.a. Full Title: Agreement between plasma and serum lipoprotein(a) [Lp(a)] measurement methods

b. Abbreviated Title (Length 26 characters): Lp(a) measurement concordance

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Christy L. Avery, Christie Ballantyne, Ron Hoogeveen, Misa Graff

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

First author [please provide a middle initial; EX: Adam L Williams]:
C **L** **A**
First name Middle initial Last name
Address: University of North Carolina Department of Epidemiology
123 W Franklin St.
Chapel Hill, NC 27516
Phone: 919/270-0174
E-mail: Christy_avery@unc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

Name: **Ron Hoogeveen**
Address: Alkek Tower (Office)
Room: ALKT-F756
Houston, TX 77030
United States
Phone:
E-mail: ronh@bcm.edu

3. Timeline: One year after approval secured.

4. Rationale:

The work described in this manuscript proposal was approved by the ARIC Steering Committee on 2/12/2024 (2023.38). Funding is provided by R01HL172887 (MPIs: Avery, Graff; subcontract PI: Ballantyne).

Lp(a) is a highly atherogenic and proinflammatory lipoprotein elevated in 1.5 billion people globally.[1-3] First described in 1963,[4] Lp(a) consists of one low-density lipoprotein (LDL)-like particle covalently bound to one apolipoprotein(a) [apo(a)] particle.[5-8] Lp(a)'s LDL-like particle is hypothesized to promote atherogenesis given its similarity to LDL. Distinctions between Lp(a) and LDL are due to apo(a), which produces Lp(a)'s size heterogeneity and unique pathophysiologic properties,[9] e.g., fibrinolysis inhibition[10,11] and transport of oxidized phospholipids that trigger sterile inflammation and calcification.[12,13] These properties have motivated observational[7,14] and genetic[5,15-17] studies that report *independent* associations between elevated Lp(a) and increased atherosclerotic cardiovascular disease (ASCVD) risk.[18-21] Several highly promising[22] Lp(a) reducing therapeutics targeting different mechanisms of action are now in pivotal clinical trials.[23-29] Acknowledging the strength of evidence linking Lp(a) with ASCVD, national and international guidelines recommend Lp(a) measurement either in individuals with moderate to high ASCVD risk or in everyone at least once.[30-33]

Prior ARIC studies measured levels of Lp(a) in EDTA plasma. Other studies have measured Lp(a) in plasma (e.g., MESA) or serum (HCHS/SOL, UK Biobank). No studies to the best of our knowledge have evaluated whether levels of Lp(a) differ between plasma or serum.[34,35] This is an important question with clinical and public health implications, and ARIC and the Ballantyne lab have previously done numerous QC studies to address this type of question for other assays (e.g., high sensitivity troponin T). We therefore propose to measure Lp(a) in both serum and plasma in 100 individuals from samples at V6. V6 was chosen because there has not been much demand for serum and plasma from these visits thus far. We will use the same Denka Seiken assay for measurement of Lp(a) as performed at V4 and V5.

In summary, these data will be useful for ARIC investigators when using ARIC data on Lp(a) in multi-cohort analyses which have measured Lp(a) in serum as compared to plasma. This work also will inform the larger body of literature that has measured Lp(a) in serum or plasma.

5. Main Hypothesis/Study Aims:

Aim: Evaluate concordance in Lp(a) measured from serum and plasma in a race and sex-balanced subsample from the ARIC V6 exam.

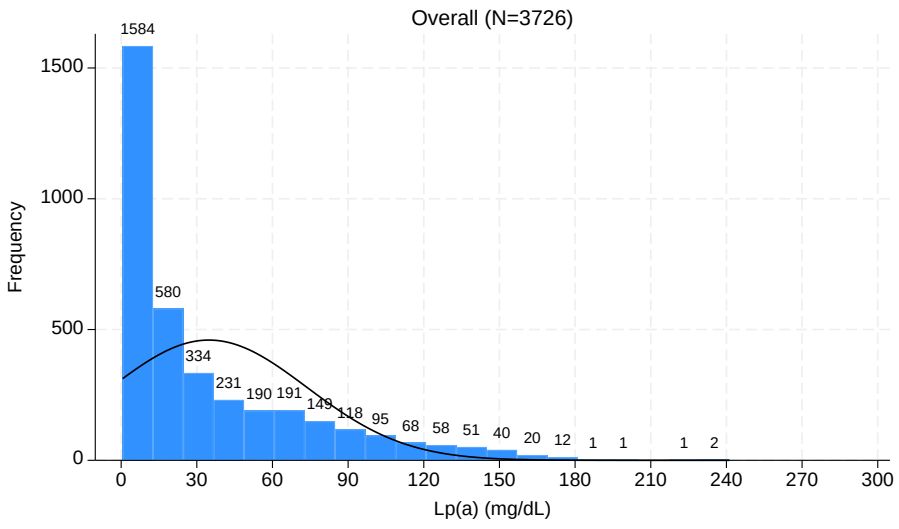
Hypothesis: There will be high concordance between Lp(a) measured in plasma and serum given findings for other lipoproteins.[36,37]

6. Design and analysis - please address the following aspects:

a) Inclusion/exclusion.

Eligible participants attended V5 and V6 and have Lp(a) measured at V5. Because Lp(a) is ~stable across the life course,[38] we can use V5 Lp(a) measures to help ensure that V6 samples are approximately uniform across the Lp(a) distribution. This approach is particularly important for Lp(a), which has an extreme right skew and a large proportion of participants with very low Lp(a) (**Figure**). To ensure adequate representation by race and sex, and to address known differences in the distribution of Lp(a) by race and sex, selection will be performed stratified by sex and race, which also ensures equal representation.

Table. Distribution of Lp(a) in n=3,726 ARIC participants at V5 who also attended V6.



b) Study design

Our cross-sectional study will measure Lp(a) in paired plasma and serum V6 samples. We will conduct analyses in the overall cohort and by race and sex.

c) Outcome and other variables of interest with specific reference to the time of their collection

We will use V5 data to select V6 participants in whom we will measure Lp(a) in stored serum and plasma specimens.

d) Summary of data analysis

Lp(a) will be measured in paired serum and plasma samples using the Denka Seikken assay. This approach will enable direct comparison of plasma and serum Lp(a) while minimizing the effects of analytical imprecision. We will calculate central tendency measures, coefficients of variation, and Pearson correlation coefficients to evaluate correlation between serum and plasma Lp(a). To examine evidence of systematic bias at high or low Lp(a) levels, we will use Bland Altman analysis.[39] Deming regression will be used to quantify concordance between the two assays. In the unanticipated event that we detect significant differences ($P<0.05$) between plasma and serum Lp(a) measures, we will derive a correction factor.[40]

e) Any anticipated methodologic limitations or challenges if present

We do not foresee any methodologic challenges or limitations. Drs. Hoogeveen and Ballantyne have extensive experience with the Denka Seikken assay and the proposed analyses. We have external funding to complete the proposed measurements and analyses.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☒ **Yes** ☐ **No**
(The file ICTDER is distributed to ARIC PIs annually, 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** ☒ **No**

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ **Yes** ☐ **No** ☒ **N/A**

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
No overlap – no study is measuring paired Lp(a) plasma and serum samples.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ **Yes** ☒ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal
☒ **A. primarily the result of an ancillary study**
☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number 2023.38__

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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