1.a. **Full Title:** Individual Participant Data Meta-analysis of Advanced HDL Lipoprotein Analysis and Cardiovascular Outcomes

b. **Abbreviated Title (Length 26 characters):** HDL lipoprotein meta-analysis

2. **Writing Group:**
   Writing group members: Alvin Chandra, Christie Ballantyne, Salim Virani, Colby Ayers, Anand Rohatgi (plus 1-2 investigators from other cohorts).

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

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3. **Timeline:**  5/2017 – 5/2019

4. **Rationale:**
   In the recent years, multiple studies have shown that HDL particle concentration is inversely associated with adverse cardiovascular events independent of HDL cholesterol (HDL-C) level. However, it remains unknown how HDL particle concentration and other advanced lipoprotein
composition measures associate with stroke or cardiovascular events in women and African Americans. A few recent cohort studies\textsuperscript{1,2} have shown that very high level of HDL-C is associated with increased mortality. It remains unclear what the effects of very high levels of HDL-C are on cardiovascular events.

By performing an individual participant data meta-analysis, our study team aims to analyze the relationship between NMR-derived advanced lipoprotein data and cardiovascular events and stroke. Additionally, we aim to analyze the relationship between traditional lipids on whole cohort and cardiovascular events to test the extreme HDL-C question. Our study team has so far obtained data from Dallas Heart Study, MESA, and we are currently waiting for data from EPIC-Norfolk. We would like to add data from ARIC.

We have submitted a proposal for ARIC data via BioLINCC and received approval. However, the data we received from BioLINCC did not have the NMR-derived lipoprotein analysis data that we needed. We later found out that these data were completed in a separate ancillary study. We are submitting this proposal in order to obtain them.

References:

5. Main Hypothesis/Study Questions:
1. HDL particle concentration is significantly inversely associated with stroke events independent of HDL-C levels.
2. HDL particle concentration is significantly inversely associated with cardiovascular events in women and African Americans independent of HDL-C levels.
3. Extremely elevated HDL-C is significantly associated with cardiovascular events.

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: Individual participant data meta-analysis

Questions 1-2
Inclusion criteria:
- 1670 members of ARIC study cohort who have NMR-derived lipoprotein particle analysis. These participants are part of a sub-study and participated in the ARIC Carotid MRI substudy in 2004–2005 (Year 18).

Exclusion criteria:
- Members of ARIC study cohort with a history of cardiovascular disease (history of myocardial infarction, stroke, arterial revascularization, heart failure, or arrhythmia) or niacin use.

Question #3:
Inclusion criteria:
- All participants in ARIC with traditional lipid data (i.e. total cholesterol, HDL-C, triglyceride).

Exclusion criteria:
- Members of ARIC study cohort with a history of cardiovascular disease (history of myocardial infarction, stroke, arterial revascularization, heart failure, or arrhythmia) or niacin use.

All Study Questions 1-3:
Key analytic variables:
- NMR lipoprotein analysis data:
  - HDL particle concentration
  - HDL particle size
  - Ratio of HDL Cholesterol/HDL Particle
  - Ratio of HDL Particle size/HDL Particle
  - LDL particle concentration
- All other clinical variables:
  - HDL cholesterol
  - Total cholesterol
  - Triglycerides
  - LDL cholesterol
  - Non-HDL cholesterol
  - Lipoprotein(a) concentration
  - HS-CRP
  - physical activity (all survey questions related to dose, intensity, and frequency to allow met-min/week calculation if not already calculated)
  - Alcohol intake (grams/week by self-report survey responses)
  - Age
  - Sex
  - Race
  - Hypertension (systolic and diastolic blood pressure, hx HTN, blood pressure medication use)
  - Diabetes (hx DM, glucose lowering medications, glucose, Hgba1c%)
  - Smoking (never, former, current, pack-years)
  - Statin use
  - Use of other lipid lowering medications
  - BMI
  - Waist circumference

Primary endpoints:
- Time to end of study period (latest follow up time point available) or time to following events:
  - Fatal and non-fatal MI
  - Fatal and non-fatal ischemic stroke

Secondary endpoints:
- Time to following events:
- Composite atherosclerotic cardiovascular disease outcome, defined as fatal MI, non-fatal MI, fatal ischemic stroke, non-fatal ischemic stroke, coronary revascularization (percutaneous coronary intervention or coronary-artery bypass grafting) or death from cardiovascular causes.
- CV Mortality and non-CV mortality

Statistical analysis plan:
HDL particle concentration will be analyzed as primarily as increasing quartiles and continuously. Hazard ratios will be reported for each quartile referenced to quartile 1 or per 1 standard deviation increase in HDL particle concentration. The associations will be adjusted for the following potential confounders: age, sex, race, hypertension, diabetes, smoking, statin use, use of other lipid lowering medications, traditional lipid measurements (HDL-C, LDL-C, triglyceride, and BMI. Additional adjustments will be made for waist circumference, physical activity, alcohol intake, hs-CRP, and lipoprotein(a) concentration.

We will use a 2-stage analysis approach. First, estimates of association will be calculated separately within each study. Then, pooling across studies will be done by the random-effects inverse variance method. Cox proportional hazard models will be used with HDL-P as the determinant and CV events (primary and secondary) as detailed above as the outcome. Additional exposure variables include the ratios HDL-P/HDL-C and HDL size/HDL-P. For question #3, we will evaluate the association of very high levels of HDL-C (defined as >60 mg/dl, 70mg/dl, and >80mg/dl in men; >80mg/dl and 90 mg/dl in women) with the same outcomes.

We will use interaction terms to explore whether any association with CV events differed according to the covariates in the models. Sensitivity analyses will impute missing values on covariates using the expectation maximization method (single imputation) for each cohort separately. We will analyze heterogeneity across the included studies using Cochran’s Q test and the I2 statistic. All statistical analyses will be performed using SAS.

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

__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)?

Relation of cholesterol and lipoprotein parameters with carotid artery plaque characteristics: the Atherosclerosis Risk in Communities (ARIC) carotid MRI study.
Virani SS, Catellier DJ, Pompeii LA, Nambi V, Hoogeveen RC, Wasserman BA, Coresh J, Mosley TH, Otvos JD, Sharrett AR, Boerwinkle E, Ballantyne CM.

We are including Dr. Ballantyne.

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 (list number* _Carotid MRI Study)_

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.

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 __x__ No.