ARIC Manuscript Proposal # 3591

PC Reviewed: 5/12/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between Low-Density Lipoprotein (LDL) Cholesterol Trajectories over the Adult Life Course and Risks of Cardiovascular Disease

b. Abbreviated Title (Length 26 characters): LDL Trajectories and CVD Risk

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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: The analyses will be completed within six months, and the full manuscript within one year, following approval of this manuscript proposal.

4. Rationale:

Low-density lipoprotein (LDL) cholesterol is a major modifiable risk factor for cardiovascular disease (CVD) and a key component of cardiovascular risk prediction algorithms.[1, 2] The majority of previous studies examining the association between LDL and CVD outcomes used absolute LDL levels, either as a single LDL measure or an aggregate LDL measure over the study period (e.g., mean or cumulative LDL).[3] Few studies have characterized the long-term patterns of LDL trajectories and their association with CVD events. Duncan et al. followed 3,875 participants in the Framingham Offspring Study for 35 years and identified 5 distinct patterns of LDL trajectories during middle age using group-based trajectory modeling.[4] The authors found that participants with long-term exposure to the highest LDL group (defined as very elevated LDL of ~ 220 mg/dL at the beginning and decreasing over time with medication) had 5-times the risk of CVD and 4-times the risk of total mortality compared to those in the optimal LDL group (LDL 80-90 mg/dL).[4] Dayimu et al. modeled the longitudinal trajectories of lipid profile (i.e., LDL, HDL, and triglycerides) jointly and examined its impact on incident CVD incident in a Chinese cohort of 9,726 participants.[5] Three distinct trajectories were identified using the multivariate latent class growth mixture model, but this study did not examine LDL trajectory independently.[5]

Those previous studies that examined LDL trajectories were limited because follow-up periods started during middle age; and as a result, the long-term LDL trajectory patterns across the entire adult life course and their association with CVD events remain less well known. Recent studies have found that LDL levels during young adulthood are independently associated with later life CVD events[6, 7], suggesting that a life-course perspective is essential when evaluating the dynamic changes of LDL levels throughout adulthood and their influence on CVD risk. Additionally, some evidence suggests that lipid levels increase rapidly in women during menopause.[4, 8] However, it is largely unknown if the longitudinal patterns of LDL differ by sex or by race/ethnicity across the adult life course. Furthermore, previous studies of CVD risk

factor trajectories mostly used group-based trajectory modeling (implemented in SAS Proc Traj) to determine trajectory patterns. Alternate methods of forming individual trajectories or trajectory categories have been developed recently, such as the Intercept-Slope Residuals on Age (ISRA) method[9], which can potentially further our understanding of LDL trajectory patterns and identify high risk groups earlier throughout the adult life course. A difference of the ISRA method compared to latent class growth methods (e.g., SAS Proc Traj) is that ISRA can provide more balanced trajectory groups whereas PROC TRAJ tends to have fewer participants in the tail groups with more extreme trajectory patterns.

Our study proposes to determine the patterns of LDL trajectories across the adult life course by sex and by race/ethnicity (white and blacks) using the ISRA method, and to examine the associations between LDL trajectories group and subsequent CVD events, including coronary heart disease (CHD), stroke, and heart failure (HF).

5. Main Hypothesis/Study Questions:

Aim 1: Determine the patterns of LDL trajectory over the adult life course stratified by sex and by race/ethnicity. We hypothesize that the patterns of LDL trajectory will be different for men and women, and for whites and blacks, throughout different periods (i.e., early, middle, and late) of the adult life course.

Aim 2: Examine the associations between different patterns of LDL trajectory and subsequent risks of cardiovascular disease outcomes, including coronary heart disease (CHD), stroke, and heart failure stratified by sex. We hypothesize that trajectory groups representing higher cumulative exposure levels of LDL over the adult life course will be associated with higher risks for CVD 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).

We have previously harmonized and pooled individual-level basic CVD risk factor and outcomes data from the main ARIC study with similar data from several other NIH-funded prospective cohort studies (ARIC ancillary study 2016.18)[7, 8]; related ancillary study proposals approved for CARDIA, CHS, MESA, Framingham Offspring, and Health ABC). The pooled data permits us to model risk across the adult years and provides a sufficient number of CVD events to support robust inferences that may be generalizable to the broader adult US population. Inclusion of ARIC will be an essential component of this work given its robust data in adult exposures, racial/ethnic diversity, meticulous follow-up, and gold-standard measures of CHD risk factors.

For this analysis, we will include participants age ≥18 years, without known CVD at baseline, and with ≥2 LDL measures. We will censor participants at statin initiation. We will use the Intercept-Slope Residuals on Age (ISRA) method to determine the patterns of LDL trajectories. The LDL trajectory patterns will be based on all available observed LDL values before the first incident CVD event. Specifically, we will use linear mixed-effects models with cubic spline for age and random intercept and slope to establish sex-specific and race/ethnicity-specific LDL trajectories. The intercept and slope form personal trajectories of LDL after removing the overall curve (spline) common to all participants. We make the assumption that the individual-specific

LDL intercept and slope hold for all ages and is throughout the age window of estimation. Trajectory groupings will be formed by stratifying the intercept and slope by tertiles, forming 9 nearly equal sized groups with either a low, mid or high intercept and low (declining), mid (flat) or high (increasing) slope.[9-11] Other methods of grouping the individual trajectories will be explored, if warranted.

To examine the associations between LDL trajectory patterns and CVD events including CHD, stroke, and heart failure, we will use logistic regression and stratify the analysis by sex or by race/ethnicity. All models will be adjusted for age at first visit, birth year, body mass index (BMI), smoking status, and cohort.

To examine the robustness and consistency of our findings, we will perform several sensitivity analyses: (1) instead of censoring participants at statin initiation, we will exclude those who ever used statin from the analysis; (2) for those reporting statin use, multiply their LDL by 1.43 to estimate untreated LDL levels, as was done by Benn et al., and Edwards and Moore;[12, 13] (3) instead of using logistic regression to examine the association between LDL patterns and CVD outcomes, we will treat each individual's LDL trajectory group assignment as one of their baseline characteristics and use the Cox model to assess the association between LDL patterns and incident CVD events. We will use age as the time scale and follow-up will start from the baseline age; (4) we will model LDL trajectory patterns by only using LDL levels measured before age 60 years, and then use Cox model to assess the association between LDL patterns and incident CVD events occurred after age 60 years; (5) further stratify the analysis by both sex and race/ethnicity; (6) repeat analyses by cohort, as well as leaving out one cohort at a time to confirm that our findings were not driven by any single study; (7) instead of using ISRA to identify patterns of LDL trajectories, we will use group-based trajectory modeling (Proc Traj in SAS) and compare findings using the ISRA method. All analyses will be performed using STATA version 16 (StataCorp LP, College Station, Texas), and SAS version 9.4 (Cary, NC).

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X___ 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 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 current derived consent file ICTDER05 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)?
We have queried the ARIC proposal database and found no prior ARIC manuscript proposals examined LDL trajectory patterns and their association with CVD outcomes.

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _)

___ 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 https://sites.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.

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