ARIC Manuscript Proposal #4075

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lifetime cholesterol trajectories and implications for familial hypercholesterolemia screening programs

b. Abbreviated Title (Length 26 characters):

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

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3. Timeline:

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

4. Rationale:

Familial hypercholesterolemia (FH) is a genetic disorder that causes severely elevated low-density lipoprotein cholesterol (LDL-C) levels from birth, leading to a significant increase in largely preventable premature cardiovascular morbidity and mortality.[1 2 3-6] In the United States (US), FH affects approximately 1.3 million (1 in 250 to 300) in the general population.[4,7] Early diagnosis and treatment of FH could lower the risk of CHD by as much as 80%.[8-10] However, the vast majority (~90%) of subjects with FH are undiagnosed, especially among children.[11]

Population-based cholesterol screening to identify possible FH cases is supported by multiple organizations including US Centers for Disease Control and Prevention (CDC),[12] National Heart, Lung, and Blood Institute (NHLBI),[13] American Heart Association/ American College of Cardiology (AHA/ACC),[2,14] National Lipid Association (NLA),[15] and American Academy of Pediatrics (AAP).[16] However, guidelines are in conflict regarding the age range and specific LDL-C cutoff for the screening. In 2011, the NLA Expert Panel on FH proposed universal screening for elevated cholesterol for suspected FH.[15] The panel suggested an untreated fasting LDL-C threshold of ≥160 mg/dl among adolescents and young adults (<20 years) and LDL-C ≥190 mg/dl among adults (≥ 20 years) for possible FH cases. The panel also suggested screening at age 2 for children with a family history of premature CVD or elevated cholesterol and all individuals should be screened by age 20 years.[15] In 2012, the NHLBI published the Integrated Guidelines for Cardiovascular Health and Risk Reduction in children and adolescents.[17] In this guideline, the panel suggested universal screening for FH at age 9-11 years and 17-21 years with fasting LDL-C ≥130 mg/dl and at and at age 20-21 years with LDL-C ≥160 mg/dl. However, in 2016, the US Preventative Services Task Force found insufficient evidence for or against childhood lipid screening in general or FH screening and the new update is still in progress. [14] In 2018, the AHA/ACC cholesterol guideline recommended universal FH screening among children aged 9-11 years and again at 17-21 years or selective FH screening among those aged 2 years and older based on family history and personal risk factors.[2] This lack of consensus on the age to screen and the LDL-C thresholds to use might be partially due to the lack of information on lifetime trajectories and distributions of LDL-C. Few studies have explored the life course trajectories of LDL-C from early childhood to the late adulthood.[18-21]

To address those gaps in knowledge, we propose to use data from the International Childhood Cardiovascular Cohort (i3C) Consortium and six US adult cohorts including Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Risk Development in Young Adults (CARDIA) Study, Cardiovascular Health Study (CHS), Framingham Heart Study Offspring Cohort (FHS-O), Jackson Heart Study (JHS), and Multi-Ethnic Study of Atherosclerosis (MESA) to (1) examine the lifetime trajectories of LDL-C and LDL-C distributions at various age periods (4-6, 9-11, 18-20, 39-41, and 49-51 years), and (2) assess the potential proportions of individuals with phenotypes that are consistent with possible FH at different ages using alternative LDL-C cutoffs overall and by sex and race/ethnicity.

5. Main Hypothesis/Study Questions:

1. What are distributions of LDL-C at different age periods (4-6, 9-11, 18-20, 39-41, and 49-51 years) and if there are any differences in LDL-C distribution by sex or race/ethnicity?
Hypothesis: We hypothesize the distributions of LDL-C will increase with age. On average, males and females will have similar LDL-C levels during childhood, but males will have higher LDL-C levels during young adulthood and middle age. For race/ethnicity, all racial groups will have similar LDL-C levels during childhood, racial minorities will have higher LDL-C levels starting young adulthood until later adulthood. Also, there will be strong tracking between childhood and adulthood LDL-C levels (i.e., children with LDL-C in the top quintile will likely have young adult and mid-life LDL-C levels also in the top quintile).

2. What are the proportions of individuals with phenotypes that are consistent with possible FH at different ages using with alternative LDL-C cutoff points or LDL-C percentile?
Hypothesis: We hypothesize that by using fixed LDL-C cutoffs (e.g., LDL-C ≥190 mg/dL), the proportions of individuals with phenotypes that are consistent with possible FH will increase with age, with very few children being classified as having possible FH cases. Alternatively, by using LDL-C percentiles instead of fixed LDL-C cut-offs, the proportions of individuals with phenotypes that are consistent with possible FH in childhood can be made identical to proportions of individuals with phenotypes that are consistent with possible FH in adulthood. By using the percentile approach, there will also be no difference in proportions of individuals with phenotypes that are consistent with possible FH comparing males and females or racial groups.

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).

Demographic variables: age, sex, race/ethnicity, study sites
Anthropometric variable: body mass index
Lipid variable: LDL-C, HDL-C, total cholesterol, lipid medication, triglycerides, fasting glucose, HbA1c
Other clinical variable: smoking status, body mass index, systolic BP, diastolic BP, use of antihypertensive medication, self-reported history of hypertension, use of anti-diabetes medication, and self-reported diabetes status

For individuals reporting use of lipid-lowering therapy at the time of LDL-C measurements, we will multiply their observed LDL-C by 1.43 to conservatively estimate untreated LDL-C levels, as implemented previously.[22]

For hypothesis one, we will first plot the mean trajectories of LDL-C values from age 3 to 80 years old. We will then examine the distribution (mean, median, and interquartile range) of untreated

LDL-C in five distinct age groups (4-6 years, 9-11 years, 18-20 years, 39-41 years, and 49-51 years). Finally, we will identify a subgroup of participants from the i3C cohort with LDL-C measures during both childhood and adulthood to assess LDL-C tracking. Specifically, we will first categorize participants into quintiles based on their LDL-C levels at two time points: (1) during childhood and adolescent years (age <18 years), and (2) during middle age (age 40-60 years). We will then calculate the proportions of individuals who have LDL-C in the top quintile during childhood who also have their LDL-C in the top quintile during middle age. We will also calculate the correlation between LDL-C during childhood and middle age, as well as the average proportions of individuals in each quintile who stay in the same quintile. All above analyses will be performed among overall population and by sex and race/ethnicity.

For hypothesis two, we will first estimate the prevalence of untreated LDL-C according to commonly used thresholds of <130 mg/dl, 130-159 mg/dl, 160-189 mg/dl, and ≥190 mg/dl. To further explore optimal LDL-C thresholds for FH screening, we will also calculate the values of untreated LDL-C levels that correspond to the top 5th percentiles (95th, 96th, 97th, 98th, 99th) of untreated LDL-C distribution in each of the 5 age groups overall and by sex and race/ethnicity.

We will perform two set of sensitivity analyses: (1) instead of using untreated LDL-C, we will repeat all analyses using the observed LDL-C values, and (2) we will limit the analysis to participants who were not taking lipid-lowering medications.

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/aricproposals/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)?

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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