ARIC Manuscript Proposal #3684

PC Reviewed: 8/11/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations of nutrient biomarkers and longitudinal lung function phenotypes in the NHLBI Pooled Cohorts Study

b. Abbreviated Title (Length 26 characters): Nutrition and PFT decline

2. Writing Group:
Writing group members: Kari North, Stephanie London, Dana Hancock, Patricia Cassano

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

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3. Timeline:
This project is a multi-cohort effort that represents the first manuscript for ARIC ancillary study 2020.04. We anticipate completing the work for this first manuscript over the course of 18 months. During the first 3 months, we will obtain the required data, prepare the data for analysis, and run preliminary models. During months 4 through 12 we will perform our proposed analyses, including subgroup and sensitivity analyses, and prepare and submit an abstract for presentation. In the final 6 months, we will develop the manuscript, preform additional analyses and revisions as needed, and submit (and resubmit) for publication.

4. Rationale:

Lung function, as measured by spirometry, increases from childhood through early adulthood and then declines naturally with age. Accelerated lung function decline increases the risk of chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the US. Environmental exposures influence lung function and alter its lifelong trajectory. Cigarette smoking, which leads to chronic airway inflammation and lung tissue injury, impairs lung function, accelerates its decline and contributes to the development of COPD. Smoking cessation attenuates the effects of cigarette smoke exposure on lung function and its decline, however former smokers remain at increased risk compared with never smokers[1].

Nutrients that modulate the inflammatory response such as vitamin D (Vit D) and omega-3 fatty acids (ω-3 FAs) can potentially mitigate lung function decline and prevent the development of COPD. Cross-sectional analyses by our research group and others have shown that higher levels of Vit D and ω-3 FAs in the blood are associated with better lung function and lower risk of COPD, especially in individuals with a history of smoking[2–6]. However, causal inference for the relation of these nutrients with long-term lung outcomes has been limited. Results from longitudinal studies have been inconsistent, with effects in some studies limited to subgroups that were not evaluated in other studies[7–13], and few randomized controlled trials (RCTs) have examined the effects of Vit D or ω-3 FAs on lung function decline in the general population. Further, determining whether Vit D or ω-3 FAs are causally related to long-term lung outcomes with RCTs may not be feasible, as many chronic diseases including COPD have long latency periods and are influenced by nutrition and other factors throughout life[14,15]. Addressing these limitations and understanding the relation between nutritional status of Vit D and ω-3 FAs and long-term lung outcomes is important for developing recommendations and dietary guidelines to slow lung function decline and reduce the public health burden of COPD.

5. Main Hypothesis/Study Questions:

We hypothesize that individuals with higher levels of Vit D and ω-3 FA biomarkers will have less lung function decline and lower incidence of chronic airways obstruction than those with lower levels of these nutrients.

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 will use both observational epidemiology and Mendelian Randomization (MR) approaches to improve causal inference for the associations of Vit D and ω-3 FA biomarker levels with lung function decline and incidence of chronic airways obstruction. Specifically, we will: a) test associations of Vit D/ω-3 FAs with longitudinal lung function phenotypes in the NHLBI Pooled Cohorts Study and b) perform the first MR studies of nutritional status and lung function decline.

<u>Longitudinal Analysis:</u>

For the longitudinal analyses, we will leverage the NHLBI Pooled Cohort Study[16], which has harmonized longitudinal spirometry data across 9 population-based US cohorts. Six of the nine contributing cohorts have existing Vit D and/or ω-3 FA biomarker data. These include the Atherosclerosis Risk in Communities (ARIC) Study, the Coronary Artery Risk Development in

Young Adults (CARDIA) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study – Offspring Cohort (FHS-O), the Health, Aging & Body Composition (Health ABC) Study, and the Multi-Ethnic Study of Atherosclerosis (MESA).

Our ultimate plan is to obtain the harmonized spirometry and nutrient biomarker data from each cohort and conduct pooled analyses across all participants. The overall sample will include all Black and White participants from these cohorts for whom spirometry, nutrient biomarker, and covariate data are available (total N~21,000 for Vit D, ~12,200 for ω-3 FAs). For ARIC, this includes all Black and White participants with spirometry measurements at visits 1, 2 and/or 5 who also have Vit D measurements (visit 2, N= ~3,150 Blacks and ~9,880 Whites) and/or ω-3 FA measurements (visit 1, N ~3,200 Whites).

For our primary analysis, we will evaluate the effect of baseline Vit D and ω-3 FA levels on the rate of lung function decline using linear mixed effects (LME) modeling, as is often done for repeated measures. We will run separate models of the effect of Vit D and each of the four ω-3 FAs (ALA, EPA, DPA and DHA) on decline in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and their ratio (FEV_1/FVC). Secondary analyses evaluating the association of baseline Vit D or ω-3 FA levels with the incidence of chronic airways obstruction, defined as FEV_1 and FEV_1/FVC both less than their respective lower limits of normal, will be performed using Cox proportional hazards and binomial regression modeling in participants without airways obstruction at first spirometry measurement.

In all models, we will account for important covariates, including age at baseline, sex, race/ethnicity, height and weight at each spirometry measurement, baseline pack-years of cigarette smoking, smoking status at each spirometry measurement, and if applicable, study site (for studies with multiple study centers). Given seasonal variation in Vit D levels, we will also adjust for season of blood draw in those analyses. Additional analyses using models extended to include interaction terms of Vit D/ω-3 FAs with age, race, sex, smoking status throughout follow-up and/or nutrient status (deficiency/insufficiency/sufficiency) will be used to evaluate whether the effect of Vit D/ ω-3 FAs on lung function decline and the development of chronic airways obstruction depends on these variables.

MR Analysis:

Our MR analysis will use summary statistics from previously published GWAS. These analyses are achieved without any additional data or analysis requests from the cohorts and provide added value to the study. Since we are not requesting data for this, this section does not describe the MR data in detail.

We will perform two sample MR[17] using existing genetic data sets, including UK Biobank and previously published CHARGE and SUNLIGHT Consortium GWAS, to generate the genetic instruments and test for causality. With this approach, we can use larger sample sizes at both stages, increasing the strength of the genetic instrument for Vit D/ω-3 FAs and the power to infer causal effects of Vit D/ω-3 FAs on lung function decline. Additionally, by obtaining genetic associations for Vit D/ω-3 FAs and lung function decline in separate, independent samples, we will decrease the risk of bias towards the potentially confounded observational estimate[18].

Our genetic instruments for each nutrient will be made by identifying variants associated with Vit D or ω-3 FAs at genome-wide significance in in previous GWAS studies, with evidence of replication in independent samples. We will evaluate linkage-disequilibrium of the identified variants, and for variants that are co-inherited we will include only the variant with the strongest

signal. Our final genetic instruments for vit D and ω-3 FAs will include all independent variants passing the above criteria.

We will then use existing data from previously published GWAS regression analyses to obtain beta coefficients, standard errors, and effect alleles for the associations of these variants with Vit D[19] or ω-3 FAs[20] and lung function decline[21]. Using these data, we will perform inverse-variance weighted (IVW) MR to estimate the causal effect of Vit D/ω-3 FAs on lung function decline. We will also perform sensitivity analyses, including MR-Egger regression, median-weighted meta-analysis, mode-weighted meta-analysis, leave one out analyses, multivariate MR, and funnel plots, to assess heterogeneity and evaluate potential bias from off-target effects of the genetic variants included. All analyses will be performed using the R packages 'TwoSampleMR' (https://github.com/MRCIEU/TwoSampleMR) and 'MRInstruments' https://github.com/MRCIEU/MRInstruments)[18]. We will ultimately triangulate our findings from the longitudinal analysis and the MR analysis, which will provide stronger causal inference than possible from previous studies.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? _x_ 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" ? _x_ 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)?

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 AS 2020.04*)
Does not involve new CHS data collection
Also uses vitamin D and omega-3 fatty acid data from AS 2009.17 and 2010.02
___ 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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