ARIC Manuscript Proposal #4433

PC Reviewed: 04/09/24 **Status:** **Priority: 2**

1.a. Full Title:

Exploring Organ Age Disparities and Risk of Chronic Diseases in a Community-Based Population

b. Abbreviated Title (Length 26 characters): Organ Aging Signatures in ARIC

2. Writing Group:

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Analyses will begin once the manuscript proposal has been approved. We anticipate that the manuscript will be written and submitted to the ARIC Publications Committee within one year of the manuscript proposal being approved.

4. Rationale:

Aging is associated with an increased risk of numerous chronic diseases due to the physiological changes that accompany the deterioration of cellular function[1-4]. As medicine and technology improve to increase global life expectancy, the burden of aging thus increases. The Global Burden of Disease 2015 Study (GBD 2015) estimated that from 1980 to 2015, the global life expectancy increased from 61.7 years to 71.8 years[5]. Studies of the underlying mechanisms of aging may help improve the development of beneficial therapies in our aging population.

Recently, it has been suggested that compared to chronological age, biological age or organ age estimated using individual-level proteomics data may be an improved quantifier of health risk[6-10]. This was motivated by observed variation in the age-related health trajectories across individuals, as well as significant associations between certain proteins in the blood, some being organ-specific, with age and age-related diseases[7,8,11-13]. Estimated biological ages or organ ages are risks for chronic diseases or mortality, providing face validity that these quantities indeed encode information about health that add to information on chronological age[6,14].

In a 2023 publication by Oh et al., three models were trained with proteomic data to estimate the ages of 11 organs (adipose tissue, artery, brain, heart, immune tissue, intestine, kidney, liver, lung, muscle and pancreas) for each individual[14]. The models were developed with different sets of circulating plasma proteins as training inputs: 1. proteins that were more highly expressed in the specific organ of interest (organ-specific), 2. proteins that were not more highly expressed in any of the organs (organismal), and 3. all proteins regardless of if they were more highly expressed in any organ (conventional). An organ age gap, defined as the difference of an individual's estimated organ age from the expected estimated organ age for peers of the same chronological age, was calculated. The organ age gap was associated with adverse outcomes in the expected direction (e.g., older estimated brain age was associated with dementia). In addition, associations with diseases specific to other organs were found as well; for instance, the kidney age gap was significantly associated with hypertension and diabetes. Oh et al.'s models have not yet been tested to estimate organ ages in the Atherosclerosis Risk in Communities cohort.

In our work, we aim to apply Oh et al.'s models to estimate organ ages in ARIC participants in visits 2, 3, and 5, and to find cross-sectional and longitudinal associations between these

estimated organ ages with health outcomes. Cross-sectional outcomes that we aim to consider include kidney function, albuminuria, body mass index (BMI), prevalent stroke, prevalent heart failure (HF), prevalent coronary heart disease (CHD), prevalent diabetes, and prevalent hypertension (HTN). Longitudinal outcomes that we aim to consider include kidney function decline, albuminuria progression, mortality incident stroke, incident HF, incident CHD, and incident HTN. We will pursue replication in other cohorts, which may include AASK, BKBC, CRIC, and Baltimore Longitudinal Study of Aging cohorts.

5. Main Hypothesis/Study Questions:

We will use Oh et al.'s organ aging models to estimate the organ age gap of 11 organs for participants within visits 2, 3, and 5.

We aim to assess the cross-sectional association between the estimated organ age gap of each organ with eGFR, BMI, albuminuria (defined with albumin-to-creatinine ratio (ACR); available only at visit 5), prevalent stroke, prevalent HF, prevalent CHD, prevalent diabetes, or prevalent HTN.

We also aim to assess the longitudinal association between the estimated organ age gap of each organ with kidney function decline (defined as 40% decline in eGFR or ESRD), ACR doubling (visit 5 as baseline only), mortality, incident stroke, incident HF, incident CHD, incident diabetes, or incident HTN.

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).

Cross-sectional associations between organ age gap and health outcomes

Study design and population

We will include participants with available proteomics data at ARIC visits 2, 3, or 5.

Exposure

Organ age gap, age, sex, race-center, eGFR, ACR, BMI, smoking status, prevalent stroke, prevalent HF, prevalent CHD, prevalent diabetes, prevalent HTN (other clinical covariates may be added in a subsequent, fully adjusted model)

Outcomes

eGFR, ACR, BMI, prevalent stroke, prevalent HF, prevalent CHD, prevalent diabetes, prevalent HTN

Statistical Analysis

At each visit, we will use either a linear regression model for outcomes that are continuous or a logistic model for binary outcomes to assess the cross-sectional associations between the organ age gaps of each organ with each adverse health outcome.

$$\text{Outcome} \sim \text{organ age gap} + \text{age} + \text{sex} + \text{race-center} + \text{other covariates}$$

For the combined data from visits 2, 3, and 5 (where one participant may appear more than once), mixed models with random intercepts to account for persons will be used to assess the cross-sectional associations between the organ age gaps of each organ with each adverse health outcome.

$$\text{Outcome} \sim \text{organ age gap} + \text{age} + \text{sex} + \text{race-center} + \text{other covariates} + (1|\text{participant})$$

To account for multiple testing, statistical significance will be evaluated using a Bonferroni-corrected threshold of $p < 0.05/(11 * \text{number of health outcomes})$.

Longitudinal associations between organ age gap and health outcomes

Study design and population

We will include participants with available proteomics data at visit 2. For each analysis of each outcome, we will exclude participants with a prevalence of that outcome at visit 2.

For sensitivity analysis, we assess the risk of each outcome with visits 2, 3, or 5 as baseline (with visits 2, 3, or 5 as a baseline (i.e. three sets of analyses from visit 2-7, visit 3-7, and visit 5-7). Participants with available proteomics data and no prevalence of the outcome of interest at visit 2, 3, or 5 respectively will be included in analyses.

Exposure

Organ-age gap, age, sex, race-center, eGFR, ACR, BMI, smoking status, prevalent stroke, prevalent HF, prevalent CHD, prevalent diabetes, prevalent HTN (other clinical covariates may be added in a subsequent, fully adjusted model)

Outcomes

40% decline in eGFR or ESRD, ACR doubling, mortality, incident stroke, incident HF, incident CHD, incident diabetes, or incident HTN

Statistical Analysis

For our main analysis for each organ, we will use time-updated Cox proportional-hazard models to assess the hazard ratios for each incident outcome. For sensitivity analysis, Cox proportional-hazard models (not time-updated) will be used instead, since organ age gaps cannot be determined for visits other than visit 2, 3, and 5.

$$\text{Outcome} \sim \text{organ age gap} + \text{age} + \text{sex} + \text{race-center} + \text{other covariates}$$

To account for multiple testing, statistical significance will be evaluated using a Bonferroni-corrected threshold of $p = 0.05/(11 * \text{number of health outcomes}) < 0.05$.

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 _X_ No

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)?

MP# 4165 Measuring organ-specific biological age using plasma proteomics and machine learning

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.

13. References

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