ARIC Manuscript Proposal #3706

PC Reviewed: 9/8/20  Status: _____  Priority: 2
SC Reviewed: __________  Status: _____  Priority: _____

1.a. Full Title: Rate of Aging and Functional Abilities in Older Adulthood: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
   Aging rate and functional ability

2. Writing Group:
   Writing group members: Yifei Lu, James Pike, Anna Kucharska-Newton, Priya Palta, Eric Whitsel, Ganga Bey, Anthony Zannas, B. Gwen Windham, Keenan Walker, Michael Griswold

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ __

First author: Yifei Lu
Address: Department of Epidemiology
123 W. Franklin Street, Suite 410
Chapel Hill, NC 27516-8030
E-mail: yifeilu@live.unc.edu

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).

Name: Gerardo Heiss
Address: Department of Epidemiology
123 W. Franklin Street, Suite 450
Chapel Hill, NC 27516-8030
E-mail: gerardo_heiss@unc.edu

3. Timeline: Anticipated completion of a manuscript within 12 months.

4. Rationale:

While individuals aged 65 and older represented 14.5% of the population in 2014, the number of older adults will double by 2060. In most societies advancing age is associated with an exponential increase in burden from many age-related chronic conditions, and the global burden of disease and disability rises as populations age.
Aging is conceptualized by geroscience as a gradual and progressive deterioration of integrity across multiple organ systems, a process that can be quantified in animal models and humans. Instead of a stochastic process towards dysfunction and ultimately death, in the geroscience one conceptual framework seeks to identify deterministic mechanisms that modulate aging and inter-individual variability in the rate of aging, characterizing aging as an adaptive process that can be amenable to modification intended to extend health span and life span.

The most effective means to reduce age-related disease burden and its societal costs is to delay the progression of multisystem deterioration to extend health span, i.e., the years of life lived free of disease and disability, although a better understanding of aging itself is needed to extend the health span. Translation of the insights into the aging processes gained from model organisms to humans has been made difficult by the long duration of the human lifespan and the diversity of the exposures proposed to influence human aging. Further, much research on aging in humans has been cross-sectional in design, and conducted among older individuals and thus of difficult interpretation. For a better understanding of aging trajectories and of eventual intervention and prevention efforts, studies of aging focused on earlier life epochs have been promoted.

Quantifying biologic age and rate of aging

Since the pace and extent of age-related changes vary among individuals at any given chronological age, the term biological aging serves to conceptualize the observations that individuals differ in manifest age as they age chronologically. Thus, measures that characterize biological or functional age separately from chronological age are needed. No optimal ways to measure inter-individual differences in aging in humans have been established. Several candidate measures of biological aging have been proposed, including telomere length, algorithms applied to genome-wide DNA methylation data, and algorithms combining information on multiple clinical biomarkers. Similarly, various algorithms have been proposed, based on multiple linear regression, principal component analysis, as well as more complex approaches, but little validation work has been reported. It is not known at present to what degree various approaches to measure biological aging assess different aspects of the aging process, i.e., different biological aging measures may reflect different underlying “hallmarks” or “pillars” of aging and the domains of the aging phenotypes. Further, validation studies of biological aging measures have focused primarily on predicting life span, whereas it is not known whether some of the proposed methods are more closely associated with health span than others.

A limitation of molecular measures such as telomere-length and epigenetic-clock algorithms is that they are typically implemented in a single tissue, whereas multi-biomarker measures of biological age, age-related homeostatic dysregulation, and pace-of-aging measures draw information from multiple systems throughout the body. Multi-biomarker algorithms have been proposed as a more accurate alternative to single-marker measures of aging. Composite measures from multiple systems may thus be better suited to reflect the hallmarks of aging and the domains of aging phenotypes, and allow for a multi-function examination of their ability to predict the development of the aging phenotypes.
Belsky and collaborators studied 7 methods to quantify biological aging in a cohort followed to midlife, quantifying telomere length; telomere erosion; 353-, 99-, and 71-CpG epigenetic clocks and the clocks’ longitudinal ticking rates; and 3 multiple-biomarker algorithms (KDM biological age, age-related homeostatic dysregulation, and the pace of aging). All epigenetic clocks matched the chronological age at which blood samples were taken and showed the expected patterns of telomere erosion and epigenetic aging according to the time elapsed between sample collections. The epigenetic clocks correlated with one another and so did the biomarker algorithms, but correlations between the epigenetic clocks and biomarker algorithms were remarkably low, as were correlations of both sets of measures with telomere length. Notably, the measures of biological aging were strongly associated with health span–related traits (balance, grip-strength, motor coordination, physical limitations, cognitive decline, self-rated health, and facial aging) whereas the molecular measures of biologic aging were not.

Health span

Considering health as a continuous, dynamic variable that changes throughout life and whose trajectory can vary in different individuals, measures of health span are intended to quantify overall health. A consensus definition of health span does not exist, considering that ‘good health’ is subjective as well as reversible (among other challenges to standardization). A common definition of health span applies to the period of life spent in good health, free from the chronic diseases and disabilities of aging, implying a measure of chronological time beginning at birth and ending at some subsequent time. The incidence of selected diseases has been proposed as a measure of an organism’s resilience and thus of progression of the aging process, indexing disease-free survival (the health span) as a phenotype directly associated with the rate of aging. Health span and survival free of major disease are related and often used interchangeably, understood to apply to age of first chronic disease, or disability-free life expectancy.

Zenin and collaborators examined the incidence of chronic diseases strongly associated with age after the age of 40 in a population of European descent and ranked the conditions by the number of occurrences. The top eight clinically manifest morbidities from the cluster, considering an individual's age, gender, genetic variation and other covariates were selected. The risk of the selected diseases was observed to increase exponentially at similar rates, with a doubling time of approximately eight years, close to the mortality risk doubling time from Gompertz’ law of mortality, and consistent with a commonality of underlying mechanisms. Health span was defined as the age of onset of the first disease from the list of the selected “Gompertzian” diseases or death.

Our objective in this manuscript is to characterize the aging-related metabolic dysregulation at Visit 2 of the ARIC cohort (baseline), and the rate of aging from mid-life to older adulthood, and relate these markers of aging to functional capabilities of older adults and to health span.

5. Main Hypothesis/Study Questions:

Are an older physiology at mid-life, indexed by multi-system metabolic dysregulation, and a faster rate of aging from midlife to older adulthood associated with:
i. An individual’s health span?

ii. Diminished physical ability in late life?

iii. Indicators of cognitive aging from midlife to older adulthood?

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).

Prospective longitudinal design with repeat measures of time-varying exposures, accounting for cohort effects and attrition.

Measurements

**Biological Age**

**Age-Related Homeostatic Dysregulation**

Age-related homeostatic dysregulation will be calculated by applying the biomarker Mahalanobis distance (Dm) method described by Cohen and colleagues to cohort members. The biomarker Mahalanobis distance method measures how deviant an individual’s physiology is relative to a reference norm, interpreting the Mahalanobis distance from the reference as an indicator of age-related homeostatic dysregulation, a sign of biological aging. We propose to use the mean of specified biomarker values from the reference population as the indicator of a ‘normal’ physiological state.

**Reference population**

A random sample stratified on sex, race-center distribution, will serve as the internal reference population of ARIC cohort members aged 48-53 years old at ARIC’s visit 2 (baseline) and free of chronic disease manifestations and/or diagnoses within the first three years of follow-up.

**Study population**

Observations measured at all scheduled visits with complete single or combined biomarkers per Dm analysis requirement.

**Biomarkers (Appendix 1)**

Age-related homeostatic dysregulation will be calculated from the following biomarkers (each standard normal transformed, e.g., log-transformation if necessary for normality, then subtracted from the mean and divided by the standard deviation):

- Body mass index (BMI), waist girth, forced expiratory volume in one second (FEV1), forced vital capacity ratio (FEV1/FVC), hsCRP, the inflammation index from biomarkers measured at visit 1 (white blood cell count [WBC], fibrinogen, von Willebrand factor, and factor VIII), HbA1c, HOMA-IR, systolic blood pressure (SBP), hs-cTnT, NT-proBNP, eGFR, high density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides.
**Dm calculation**

Dm is a measure of multivariate statistical distance from a multivariate normal distribution, following the formula:

\[ Dm(x) = \sqrt{(x - \mu)^T S^{-1} (x - \mu)} \]

where \( x \) is a vector of biomarker values for a given participant at a given visit. \( \mu \) and \( S \) are calculated from the reference population, denoting as the reference mean and variance-covariance matrix, respectively, for the equivalent-length vector of biomarkers.

In our primary analyses we will calculate Dm using the full set of the biomarkers listed above for each of the observations at all visits. Missing biomarkers measures will be imputed whenever possible. Given its right-skewed distribution with a lower bound at zero, Dm will be log-transformed and scaled by its standard deviation. As a sensitivity analysis to confirm the robustness of biomarker selection we will repeat the Dm calculation for each biomarker and all available combinations.

**Outcomes**

**Diminished Physical Capacity**

Physical capacity will be assessed from (a) short physical performance battery (SPPB), grip strength, and the two-minute walk (2MW) test, and (b) self-reported functional status (ability to: i. do usual activities; ii. walk half a mile; iii. walk up and down stairs; iv. do heavy work).

Physical function was examined at ARIC visit 5-7 using grip strength and the SPPB, a summary measure of performance in three components: repeated chair stands, standing balance, and gait speed. Based on population-based norms, 0 (poorest) to 4 (best) was assigned to each component, yielding a composite score ranging from 0 to 12. A component score \( \leq 2 \) or SPPB score \( \leq 6 \) was considered to be poor physical function.

Specifically, participants were timed up to 60 seconds (s) to repeat five times standing from a seated position as quickly as they can with arms folded across their chest. Participants were scored 0 points if unable to accomplish, 1 point if it took 16.7-<60s, 2 points if 13.7-<16.7s, 3 points if 11.2-<13.7 s, and 4 points if \(<11.2s. For the standing balance test, the time (up to 10 seconds) that the participant can hold each position (side-by-side, semi-tandem, tandem) was recorded. Beginning with semi-tandem stand, if unable to hold this position for 10s, the participants then were tested on side-by-side stand. Those who completed semi-tandem were assumed to be able to complete side-by-side and subsequently evaluated in the tandem stand. 1 point was assigned for completion of the side-by-side stand, another point for completing the semi-tandem stand, and 1 point for holding tandem position 3-<10s. Two points were given for holding tandem position 10s. Time to walk 4 meters at the participant’s usual pace was measured. Participants were scored 0 point if unable to accomplish, 1 point if it took \( \geq 8.70s \), 2 points if 6.21-<8.70s, 3 points if 4.82-<6.21s, and 4 points if \(<4.82 \text{ s.} \)
Grip strength in kilograms of force was measured at ARIC visit 5-7 using a Jamar Hydraulic Hand Dynamometer in participant's dominant hand. Two trials were taken for each participant and the better one was used for this analysis. If participants only completed one trial, the single trial result was used.

The 2MW, a measure of functional endurance, was examined at visit 6 and 7. The 2MW records the distance walked on a 50-foot course (out and back, marked by cones at each end) in two minutes. Participants were instructed to slow down or stop if needed but to continue walking once able. The test was discontinued and the timer was stopped if the participant experienced chest pain/pressure/tightness, then the test was marked as ended incompletely with the reason for doing so. Once the 2 minutes concluded, the participant was instructed to stop and remain stationary while the end point was marked. The participant’s raw score is the distance walked in two minutes, reported in feet.

Functional status was assessed during routine annual telephone interviews from 1993 through 2007 and from 2015 until the present using a modified Rosow-Breslau questionnaire consisting of four questions: 1) Are you able to do your usual activities, such as work around the house or recreation? 2) Are you able to walk up and down stairs without help? 3) Are you able to do heavy work around the house, such as shoveling snow or washing windows? 4) Are you able to walk half a mile without help? A composite functional status score by summing up the response (yes=1, no=0) of aforementioned 4 questions were ranging from 0 (poorest) to 4 (best).²¹,²²

Cognitive Aging

We propose to use the 3 standardized neuropsychological assessments measured at visits 2, 4, and 5 (Delayed Word Recall Test, the Digit Symbol Substitution Test, and the Word Fluency Test), converting test scores from each visit to z scores based on the visit 2 population mean (SD). A composite factor score will be created as the sum of the 3 test-specific z scores and standardized to the visit 2 composite z score mean and SD for all participants.

Subjective cognitive complaints will be ascertained from repeated assessments of cognitive complaints (Do you feel as if your memory is becoming worse? Does this worry you?).

Health span

Following the approach developed by Zenin and collaborators in the UKB cohort we will estimate the age at onset of the first among a cluster of clinical health event manifestations that increase exponentially with age, as an individual’s health span.¹⁷ The top eight morbidities strongly associated with age after the age of 40 that are defined by a discrete clinical outcome, as ranked by the number of occurrences in the UKB include heart failure, cancer, myocardial infarction, chronic obstructive pulmonary disease, diabetes, stroke, dementia, and death. The risks of these conditions increase exponentially with age at approximately the same rates.

Analytic Approach

Association between Dm and age
The association of Dm with age will be evaluated using linear mixed effects regression models by fitting linear and quadratic age terms in addition to a priori selected biomarkers of metabolic dysregulation. This will allow for the assessment of non-linear associations. We propose to employ random intercepts and slopes to account for individual differences and use an unstructured correlation matrix.

\[ D_{m,i} = \beta_0 + \beta_1 \times age_i + \beta_2 \times age_i^2 + b_{0,i} + b_{1,i} \times age_i + \varepsilon_i \]

where \( \beta_0 \) denotes mean level of Dm, and \( \beta_1 \) and \( \beta_2 \) are Dm changes over age at the population level. \( b_{0,i} \) and \( b_{1,i} \) are the random deviations of individual \( i \) from the population averaged Dm and its change with age, respectively. \( \varepsilon_i \) is a residual error term. We will store \( b_{0,i} \) and \( b_{1,i} \) for each individual as predictors for the subsequent analyses.

In sensitivity analyses to explore the importance of including a given biomarker in Dm calculation to model fit, we will repeat the aforementioned analyses for all biomarker combinations. Then we will extract the Akaike information criterion (AIC) as the dependent variable and run univariate regression models on presence/absence of a given biomarker. A greater \( \beta \)-coefficient will indicate the importance to include the corresponding biomarker in estimating the age-related homeostatic dysregulation. As sensitivity analysis, this process will be repeated using the Bayesian information criterion (BIC).

We will use Dm or estimated individual Dm trajectory parameters (\( b_{0,i} \) and \( b_{1,i} \)) assessed above as the predictors for the health outcomes:

a. Association of Dm with diminished physical ability in late life

Associations of midlife metabolic dysregulation and rate of aging (Dm at visit 2 or \( b_{0,i} \) and \( b_{1,i} \), either continuously or categorically) with poor physical functional performance (i.e., SPPB score <6 points) at visit 5 will be quantified using multivariable logistic regression model, negative binomial regression will be used for SPPB modelled over a full spectrum of 0-12 as outcome, and linear regression model if physical function measures are modelled continuously (i.e., gait speed in m/s). Whenever possible, the associations with physical function change over visit 5 to 7 (i.e., SBBP change from visit 5 to 7, and 2MW change from visit 6 to 7) will be estimated as well.

We propose to use generalized estimating equations with an unstructured correlation matrix and robust variance to estimate the difference in population-averaged functional status score change over time according to midlife physiologic dysregulation and rate of aging. Two models will be considered. The first model will regress on Dm updated at all available visits. The second model will include individual midlife metabolic dysregulation and rate of aging parameters (\( b_{0,i} \) and \( b_{1,i} \)); again, those parameters will be considered as continuous and as categorical variables. Time (age) on study will be modeled with a 2-piece linear spline with a
knot at year 65. Interaction terms between the exposure and each of the 2 time spline terms will be included to examine whether rates of functional status change differ by level of exposure.

b. Association of Dm with indicators of cognitive aging from midlife to older adulthood

The trajectory of cognitive change over time across midlife physiologic dysregulation and rate of aging will be estimated using the same method proposed for functional status. All models will be adjusted for age at visit 2, sex, race, education, and ApoE. All participants with cognitive data available at baseline (visit 2) will be in the analytic set. Informative missingness will be addressed through multiple imputation by chained equations (MICE) in longitudinal models where appropriate.

c. Association of Dm with health span

c.1 Incidence of disease calculation

We will estimate incidence of the 7 selected chronic diseases, risk of death (the mortality rate) and health span across Dm categories. The disease incidence rates will be calculated independently (cohort members that have more than one condition during follow-up period will counted for every disease, except for health span which is defined as the first event occurred.

Incident event determinations will follow the definitions used by the ARIC study. The age of first occurrence will be defined for each condition, ascertained from various sources: self-reported information from annual/semiannual follow up calls, cohort examination visits, the occurrence of a diagnostic code in hospital discharge records, and death certificates. The minimal age will serve as the age the health span terminates. In calculating disease incidence rates each participant is counted regardless of other disease earlier in life (individuals may have different event times for different conditions).

Computation of the incidence rate at a given age \( t \) will consider the set of participants who are free of the specified health conditions at age \( t \) and whose health status is available in the whole age range. The maximum follow-up age does not coincide with the age at the diagnosis and is inferred from the study data. An underlying assumption is that the diagnosis of these diseases did not influence the enrollment, which is likely the case except for mortality; the mortality rate calculation may thus require a correction.

c.2 Association of Dm with health span and lifespan

A Bayesian natural history model will be used to describe the transition rate from normal to onset of the first clinical outcome (health span),\textsuperscript{23} to the disease diagnoses, to a cluster of health event manifestations, then to death (lifespan) based on the joint modeling of
longitudinal Dm levels, age at the health span terminates, and clinical health event manifestations. The modeling procedures are presented in the following form:

**c.2.1. Longitudinal Dm - Dm level**

\[ D_{m,it} = \varphi_i(t) + \varepsilon_{it} \]

where \( \varphi_i(t) = b_{0,i} + b_{1,i} t + b_{2,i} (t - t_{i0})^+ \)

\[ \varepsilon_{it} \sim N(0, \sigma^2) \text{ and } x^+ = \max(x, 0) \]. Function \( \varphi(.) \) describes the true growth of the Dm. The growth of Dm is constant until disease onset at age \( t_{i0} \) which in turn induces a change in the Dm trajectory.

**c.2.2. Time to transition and to clinical diagnosis**

\[ \lambda_0(t) = \gamma_0 t, t > 0 \]

\[ \lambda_A(t) = \begin{cases} 0, & 0 < t \leq t_{i0} \\ \gamma_A Y(t), & t > t_{i0} \end{cases} \]

\[ \lambda_c(t) = \begin{cases} 0, & 0 < t \leq t_{i0} \\ \gamma_c Y(t), & t > t_{i0} \end{cases} \]

Where \( t_{i0}, t_{ic}, t_{iA} \) are disease onset, disease diagnosis, and multiple disease manifestations, respectively, and \( \lambda_0, \lambda_c, \lambda_A \) denotes corresponding hazard function. The assumptions made here are 1) the hazard rate for the onset of disease increases linearly with age; 2) the cumulative hazard function for \( t_{ic}, t_{iA} \) depends only on the ratio of true Dm increment and annual Dm change rate \( (b_{1,i} + b_{2,i}) \).

**c.2.3. Hierarchical model for the growth rate**

\[ b_{ij} \sim N(\beta_j, \sigma_j^2) \text{ and } \beta_j \sim N(m_j, \nu_j^2) \]

\[ 1/ \sigma_j^2 \sim \text{Gamma}(a_{\sigma_j}, b_{\sigma_j}) \text{ and } 1/ \sigma^2 \sim \text{Gamma}(a_\sigma, b_\sigma) \]

\[ \gamma_0 \sim \text{Gamma}(a_0, b_0), \gamma_c \sim \text{Gamma}(a_c, b_c), \text{and } \gamma_A \sim \text{Gamma}(a_A, b_A) \]

Then several alternative specifications for the hazard functions was applied for \( t_{i0}, t_{ic}, t_{iA} \). And we repeated this analysis for the different clinical event manifestations and by sex, race.

**Potential Limitations**

Using health span relies on accurate information regarding the age of onset of the diseases considered. The actual date may be unknown since subclinical disease is common and diagnosis may lag behind onset; this difference likely leads to a systematic bias towards later ages. Cancer, diabetes, dementia, COPD, and heart failure typically develop gradually and accurate
determinations of their onset are difficult. Clinically manifest MI, stroke and death likely have the smallest lag between the condition onset and corresponding diagnosis or event. Further, information on age at onset is obtained from different sources, such as self-report, examinations conducted at varying time intervals, hospital records and death certificates.

If the discrepancy between the actual and the reported ages is random the incidence statistics still provide a good estimate of the real incidence rates, with reductions in statistical power. Some bias – probably negative – is likely to be present in incidence rate estimates.

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.cscce.unc.edu/aric/mantrack/maintain/search/dtSearch.html

_____ X_____ Yes  _____ No

found

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)?

None found
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

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

__X__ 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.csc.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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References:


