

ARIC Manuscript Proposal #3470

PC Reviewed: 9/10/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Defining and Measuring Physical Resilience in a Longitudinal Cohort: the ARIC Study

b. Abbreviated Title (Length 26 characters):

Physical Resilience

2. Writing Group:

Writing group members: B. Gwen Windham, James Henegan, Matthew McMullan, Chad Blackshear, Anna Kucharska-Newton, Priya Palta, Jennifer Schrack, Karen Bandeen-Roche, Thomas H. Mosley Jr., Michael E. Griswold others welcome.

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

First author: B. Gwen Windham

Address: UMMC
2500 N. State St
Jackson, MS 39216
Phone: 601-984-5645
E-mail: gwindham@umc.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: **B. Gwen Windham**
Address: Department of Medicine, Division of Geriatrics
2500 N. State St
Jackson, MS 39216

Phone: 601-984-5645 Fax: 601-984-5783
E-mail: gwindham@umc.edu

3. Timeline:

Writing and analyses to begin immediately following manuscript approval.

4. Rationale:

Physical resilience has been defined as the ability to recover function or resist functional decline after being exposed to a stressor.^{1,2} Resilience may contribute to better quality of life, less healthcare utilization and lower healthcare costs. An increasing number of stressors occur with age, highlighting the need to understand mechanisms underlying resilience (or lack thereof). Experts have suggested that the process we commonly think of as aging may in fact be more attributable to increased susceptibility to damage from stressors as resilience processes wear down; aging might look very different if resilience processes could be repaired.² Identifying protective factors and mechanistic pathways to resilience should translate to the development of interventions to promote physical resilience. In addition, identifying individual patients who may not be resilient to a planned stressor exposure, for example, elective surgical procedures could guide clinical decision-making.

While the concept of physical resilience has accrued increasing attention, few substantive advances have been made in this field, and several knowledge deficits remain. One missing structural element is how to precisely define and measure physical resilience. From its conceptual basis, physical resilience is comprised of both a functional outcome measure, such as gait speed, strength or robustness (i.e. from the frailty literature), and the paired occurrence of a functional stressor, such as a fall, hospitalization, or lack of social support systems. Thus, while several different functional measures have been proposed as outcomes following specific stressors, and several different stressors have been proposed that may affect specific functional outcomes, a gap exists in how or why one would choose particular stressor-resilience outcome pairings. We seek here to help move the discussion forward by examining foundations of how to construct such recommendations.

The three functional and three stressor examples given above would result in six stressor-resilience measure pairings alone, e.g. (1) fall stressor-gait speed resilience; (2) fall stressor-robustness resilience; (3) hospitalization stressor-gait speed resilience; (4) hospitalization stressor-robustness resilience; (5) poor social support stressor-gait speed resilience; (6) poor social support stressor-robustness resilience. Different pairings of stressors and resilience measures may not identify the same people as resilient, and some stressors may not distinguish between resilient and non-resilient people across outcomes. In fact, there may be no overarching physical resilience phenotype, as this may be too non-specific. Distinct phenotypes that combine a specific functional outcome of interest with a specific stressor may be a better framework to examine resiliency. There may be, for instance, a mobility – hospitalization resilience phenotype that is distinct from a mobility – fall resilience phenotype. Similarly, choosing appropriate stressors for a particular functional outcome is important. When rates of good function are similar between groups who do and do not experience a potential stressor, this would suggest that the proposed stressor lacked differentiating effects to examine resiliency on that outcome. In this case, physical resilience may not be an informative phenotype to study for that particular outcome-stressor pairing.

There is currently a lack of guidance on such nuances of measuring and defining physical resilience and the impact of various outcome-stressor pairings. Clarity on determining optimal stressor-resilience pairings may lead to more consistent findings and interpretations of results across studies. In addition, this clarity may help find better determinants of resilience that could identify persons more likely to be resilient or non-resilient. For a determinant to aid clinicians in identifying patients likely to be resilient or not, we propose the determinants should be identified for specific stressor-resilience pairings.

In this study, we propose to examine different physical resilience measures using functional and strength outcomes measured before and after a variety of pre-defined stressors. We will characterize differences in resilience prevalence across different outcome-stressor pairings to determine which pairings optimally distinguish resilient and non-resilient persons. To demonstrate the added importance of stressor-resilience pairings, we will examine the relationships of the pairings to important downstream outcomes such as mortality, the ability to live independently and later hospitalizations. Lastly, we will compare clinical, sociodemographic, and biomarker characteristics across physical resilience measures to identify resilience determinants that yield insights into at-risk persons for given outcome-stressor pairings and potentially identify mechanistic pathways to specific physical resiliencies.

The clinical implications of this work relate to the potential to define physical resilience more clearly with respect to specific functional outcomes and stressors used to define resilience. This study will set a foundation for future studies to discover biologic underpinnings of resilience and potential interventions to improve resilience.

5. Main Hypothesis/Study Questions:

- 1) To characterize influence of functional outcome-stressor pairings on resilience:
 - a. Individual (*specific*) measures for physical resilience definitions:
 - i. Functional outcomes (pre- & post-stressor, e.g. at V5 and V6): individual measures from specific objective functional assessments (gait speed, balance, lower extremity repeated chair stands, grip strength)
 - ii. Stressors (e.g. between V5 & V6): individual measures available
 1. AFU: falls, fractures, depression, social support, loss of spouse
 2. Surveillance: myocardial infarction (MI), heart failure (HF), new coronary heart disease (CHD), stroke, cancer
 - b. Alternative (*broad*) measures for physical resilience definitions:
 - i. Functional outcomes (pre- & post-stressor, e.g. at V5 and V6): measures incorporating multiple aspects/domains (SPPB, robustness [in contrast to frailty], self-reported function).
 - ii. Stressors (e.g. between V5 & V6): multiple stressors grouped together
 1. AFU: any reported hospitalization
 2. Surveillance: any cardiac stressors (MI, HF, CHD)
- 2) To examine associations of physical resilience measures on later (post-resilience determination) outcomes of mortality, institutionalization, future hospitalizations, mobility impairment or decline using post-resilience measure gait speed, balance, chair stands, inability to complete the 2 minute walk, and dementia
- 3) To examine clinical, sociodemographic, and biomarker determinants of physical resilience measures
 - a. We hypothesize that resilience will be associated with younger age, male sex, lower BMI, lower inflammation (CRP and galactin-3), lower cardiac biomarkers (Troponin T, Troponin I, and N-terminal pro-B-type natriuretic peptide), better

glucose metabolism, higher physical activity, higher income, higher education, and better neighborhood SES.

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).

Study design

Physical Resilience: We will define physical resilience using multiple definitions according to individual objective functional measures that are available at more than one timepoint, e.g. Visit 4, Visit 5, and/or Visit 6, as described below among participants who experienced a stressor between visits in question. For example, self-reported functional measures are available at visits 4 and 6 as well as in some AFU or sAFU calls.

- (a) Gait speed ≥ 1 m/second
- (b) Balance (derived sppb balance score ≥ 4)
- (c) Chair stand (derived sppb chair score ≥ 4)
- (d) We will also examine an alternative definition in which participants' gait speed at visit 6 was ≥ 1 m/second, regardless of visit 5 gait speed (maintained or improved gait speed). We will further examine participants with this pattern by comparing the degree of change, and characterizing details of potential outliers, e.g. notes from examiners, other objective metrics of functional performance, as additional evidence for resilience.
- (e) "Robust" at V5, experienced a stressor, and remained "robust" at V6.
- (f) We will also examine an alternative definition among those who were classified as "pre-frail" at V5, experienced a stressor, and were "robust" at V6. Given the very poor performance among participants categorized as "frail" and the extremely low probabilities of participants classified as "frail" becoming "robust" (potentially a measurement error), participants who were "frail" at V5, but improved to "prefrail" or "robust" status will not be considered physically resilient.

Stressors: Stressors that occur between two visits (e.g. V5 and V6), will be categorized into stressor groups as follows: Any Hospitalization, Cardiac, Physical, Social, Cognitive, Overall Health, Psychological, and Stroke. We will examine individual stressors and also combine similar stressors into a binary stressor group (absent/present). These are described in detail below.

Hospitalization:

- self-reported in annual follow up calls
- Elective procedures (via ICD9 codes)

Cardiac: Adjudicated diagnoses of myocardial infarction (MI), heart failure (HF), and Coronary Heart Disease (CHD) per protocols in ARIC.

Physical: Self-reported falls, fatigue, fractures, and chronic pain.

- Falls will be classified as present if participants responded “yes” to the following question: “In the past 12 months, did you fall?” We will also consider multiple falls (“In the past 12 months, how many times did you fall?”), severity of falls (“For the most serious fall, “Did you have to limit your activities because you were injured from this fall?” and “From this fall, did you have an injury that required you to see your doctor?”)
- Fatigue will be assessed by: “In the past 7 days:” “How often did you feel tired?” “How often did you experience extreme exhaustion?” “How often did you run out of energy?” “How often were you too tired to think clearly?” “How often were you too tired to take a bath or shower?”
- Fractures will be ascertained from hospitalization ICD-9 codes. We will classify fracture as present/absent any fracture.
- Chronic pain was assessed by: “When was the last time you experienced pain?” “Think of the last time you experienced pain, please give me a number from 1 to 10 to indicate the intensity of your pain, where 1 means no pain at all and 10 means the worst pain imaginable.” and “How often do you experience pain?”

Social: defined by participants that were widowed or had a low support system, assessed by answering “no” to “Can you count on anyone to help you when you need to make difficult decisions or talk over problems?” or “Can you count on anyone to help you with daily tasks like grocery shopping, housecleaning, cooking, telephoning, or giving you a ride?”

Cognitive: defined as self-reported memory complaints by answering yes to “Do you have any complaints concerning your memory?” “Do other people find you forgetful?” “Do you ever forget names of family members or friends?” “Do you often forget where things are left?” “Do you often use notes to avoid forgetting things?” “Do you ever have difficulties in finding particular words?” “Did you ever lose your way in your neighborhood?” “Do you think more slowly than you used to?” “Do your thoughts ever become confused?” or “Do you have concentration problems?”

Psychological: defined as self-reported depressive symptoms by answering “yes” to “During the past month, have you been bothered by feeling down, depressed or hopeless?” or “During the past month, have you been bothered by little interest or pleasure in doing things?”

Stroke: Stroke occurring between visits will be defined using adjudicated stroke events.

Downstream Outcomes:

We will examine “downstream” outcomes occurring after the specific outcome-stressor pairing resilience determination including: mortality, future institutionalization, future hospitalizations, mobility impairment or decline, poor gait speed, balance, chair stands, inability to complete the 2 minute walk, and dementia.

Determinants/Covariates/Comorbidities:

Age, sex, race-center, education, and income were self-reported at V1. Diabetes, hypertension, heart failure, stroke history, smoking status, BMI/obesity, cancer status, and biomarkers will be extracted from the pre-stressor visits.

- Cancer was self-reported in the annual follow up, assessed by: “Since we last contacted you has a doctor said you had cancer?” We will include all cancers with plans to examine individual cancers depending on sample sizes. This information will be derived from “Can you tell me in what part of the body the most recently diagnosed cancer was located?” and “What is the approximate date the cancer was diagnosed?”
- Obesity will be defined as a BMI greater than or equal to 30, measured as $(\text{weight in kilograms})/(\text{height in meters})^2$.
- Diabetes mellitus will be defined as self-reported, taking medications, nonfasting glucose greater than 200 mg/dL, or fasting glucose greater than 125mg/dL.
- Hypertension will be defined as self-reported, the use of anti-hypertensive medication, measured clinical readings of a systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure of greater than 90 mmHg.
- Prevalent CHD will be defined per ARIC protocol

Biomarkers: measured at V5 and defined under four categories: Inflammation, Cardiac, Kidney, and Glucose:

- Inflammation: CRP and Galactin-3
- Cardiac: Troponin T, Troponin I, and pro-BNP
- Kidney: Estimated GFR in ml/min/1.73m² using the CKD-EPI equation calculator
- Glucose: Glucose and fructosamine

Inclusion Criteria: All participants with functional outcomes

Exclusion Criteria: None. Some participants will not have data on all physical resilience measures but may have some from AFU calls even if they did not come to the clinic exam. Therefore, we will not plan to exclude participants for this study.

Limitations: The timing of stressor-resilience pairings will likely differ across participants. Some stressors, e.g. hospitalizations and procedures, will have dates, and we will incorporate timing of such events in the analysis. We anticipate some stressors and some resilience measures will have small sample sizes. We anticipate having different sample sizes across resilience-stressor pairings.

Statistical Analysis:

Exploration:

Initial stages of analyses will involve data cleaning, variable development, and exploratory data analyses (EDA). Graphical EDA will examine the nature and extent of potential nonlinear relationships between outcomes and continuous covariates using smoothing splines and surfaces.

Stressor-function pairings for resilience definitions:

Objective functional assessments (gait speed, robustness, etc.) will initially be categorized into trichotomous (good/poor/dead) functional measures at each visit. Stressors (heart failure, hospitalizations, etc.) and their associated timings of occurrence will be identified. Following standard resilience definition frameworks, for each stressor-function pairing, participants with good earlier functional assessments who are recorded as having experienced an intermediary stressor will be classified as resilient if they have good later functional measures, non-resilient (alive) if they have poor later functional measures, and non-resilient (dead) if they have died after the stressor and within the later visit window. Notationally, for the i^{th} participant at time t , let functional measure M be defined as $M_{it} = (2:\text{good}, 1:\text{poor}, 0:\text{dead})$ and stressor $S_{it} = (1:\text{occurrence}, 0:\text{no occurrence})$. Then for any triplet of sequential times $t = (t_1 < t_2 < t_3)$, resilience can be defined as $\mathbf{R}_{it} = (M_{it3}=2 \mid S_{it2}=1, M_{it1}=2)$, non-resilience (alive) as $\mathbf{R}_{it} = (M_{it3}=1 \mid S_{it2}=1, M_{it1}=2)$ and non-resilience (dead) as $\mathbf{R}_{it} = (M_{it3}=0 \mid S_{it2}=1, M_{it1}=2)$, thus the resilience measure $\mathbf{R}_{it}$, mirrors the functional measure definition at the third sequential time (M_{it3}) after conditioning on a previous good functional measurement and an intermediary stressor occurrence.

In many resilience studies, those with poor earlier functional measures ($M_{it1}=1$) and those who do not experience an intermediary stressor ($S_{it2}=0$) are ignored in analyses as resilience is undefined for these participants in the standard framework above. We believe that while these participants should be treated differently from those fitting the standard resilience framework, they remain useful to examine. For example, defining the probability of a good functional measure at the later visit as a function of stressor occurrence, $p^s_{it} = \Pr(M_{it3}=2 \mid S_{it2}, M_{it1}=2)$, we have that the probability of a good later functional measure following a stressor occurrence is $p^1_{it} = \Pr(M_{it3}=2 \mid S_{it2}=1, M_{it1}=2)$, which is the resilience probability $R_{it} = p^1_{it}$; this can then be naturally compared against the probability of a good later functional measure when there is no intermediary stressor occurrence $p^0_{it} = \Pr(M_{it3}=2 \mid S_{it2}=0, M_{it1}=2)$. For a given functional measure, when there is a large difference (on the absolute or relative scale) between the probabilities of good later functional measures for those who do not experience a certain stressor vs those who do, ($\Delta_s = p^0_{it} - p^1_{it}$; $RR_s = p^0_{it}/p^1_{it}$; etc.), then that stressor may have an exceptional effect on a person's ability to retain or regain their function following the stressor and resilience may indeed be an important foundational element for the pairing of that particular functional measure and stressor. When there is no difference in the probabilities of later good functional measures for those who do versus do not experience the intermediary stressor ($p^0_{it} = p^1_{it}$; $\Delta_s = 0$; $RR_s = 1$) then that particular stressor may be said to not substantively affect the particular function under study, i.e. that particular stressor-function pairing may be less useful for resiliency examinations. The distance between p^0_{it} & p^1_{it} may be estimated easily using Generalized Linear Model (GLM) approaches with $g(p^s_{it}) = X\beta + \alpha(S_{it2})$, with the link function $g()$ chosen to represent the scale of interest such as log (for relative risks, RR), logit (for odds ratios, OR) or identity (for absolute differences) and representing the distance on the appropriate scale. Timings between intermediary stressors and later functional measures may also be

accounted for within this framework through supplementary inclusions into $X\beta$ and α . Each stressor-function pairing may then be “importance ranked” for resilience examinations using the vector of estimated α ’s corresponding to the stressor-function pairings under consideration.

We note briefly here that there exists a statistically optimal domain for resilience stressor-function pairings whereby the probabilities p^0_{it} & p^1_{it} are relatively differential, but where p^1_{it} and the number experiencing the stressor are both large enough to warrant resiliency examinations (otherwise there are not enough resilient individuals for meaningful examination).

Downstream outcome associations with physical resilience across stressor-function pairings: GLMs will be used to examine how resilience versus non-resilience (alive) classifications are associated with outcomes that occur after resiliency determinations (downstream outcomes). Appropriate distribution and link functions will be chosen for each downstream outcome.

Determinants of physical resilience across stressor-function pairings:

Determinants approach 1 (multinomial models): for each resilience definition (defined by individual stressor-function pairings), we will use multinomial regression models to examine potential determinants of the trichotomous resilience measure R_{it} . (resilient, non-resilient (alive), non-resilient (dead)). Time between intermediary stressors and resiliency determination will be examined in these models. Inverse probability of attrition weighting (IPW) will be used to examine potential selection bias due to cohort attrition (missingness).

Determinants approach 2 (SEM): for each resilience definition (defined by individual stressor-function pairings), we will investigate the use of structural equation models (SEM) to expand the view of a determinant into a path based approach whereby each determinant may be associated with resiliency through (1) effects on early good functional measure probabilities (M_{it1}), (2) effects on stressor occurrence (S_{it2}), and (3) effects on later resilience probabilities (R_{it}). Time between intermediary stressors and resiliency determination will be examined in these models. Inverse probability of attrition weighting (IPW) will be used to examine potential selection bias due to cohort attrition (missingness).

Additional elements:

Alternative approaches such as using full continuous functional assessment data in resiliency measures will be examined. Survival and selection approaches will be examined to account for differential stressor timing. Shared parameter models (SPM), multiple imputation (MI) and/or inverse probability of attrition weighting (IPW) will be used to examine potential selection bias due to cohort attrition (missingness).

7.a. Will the data be used for non-CVD analysis in this manuscript? ☒ Yes ☐ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ☒ Yes ☐ No

(This 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 ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

☒ 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)?

There are no MP on physical resilience. However, the following relate via the focus on physical function and frailty:

MP 2383 Midlife Life's Simple 7 and Late Life Physical Function

MP2465 Operationalizing Frailty in the ARIC Cohort

MP2791 Association of Life's Simple 7 in Midlife and Late Life Frailty

MP2254 Relationship of Adiposity Trajectories with Late Life Physical Function

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ____ No

11.b. If yes, is the proposal

☒ A. primarily the result of an ancillary study (list number* 2008.06)

____ 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 at <https://www2.csc.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.

1. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2015;71(4):489-495.
2. Hadley EC, Kuchel GA, Newman AB, Workshop S, Participants. Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2017;72(7):980-990.