1.a. Full Title:
Vital exhaustion in midlife as a predictor of frailty in late-life: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Midlife vital exhaustion and frailty

2. Writing Group:
Alison Huang, George Rebok, Jeremy Walston, Priya Palta, B. Gwen Windham, Rebecca Gottesman, Keenan Walker, others welcome

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

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3. Timeline:
6-9 months: analysis of data
6-9 months: writing of manuscript
4. **Rationale:**

Frailty is a clinical manifestation of aging, characterized by multiple phenotypes, particularly weight loss and loss of muscle mass, weakness, exhaustion, slowness, and low energy expenditure.\(^1\) Described as a “transition phase between successful aging and disability,” onset of frailty often precedes a debilitating chain of negative health events that can lead to worsened disability and death. Recently, frailty has been identified by the World Health Organization as an emerging public health priority.\(^2\)

One potential early marker for frailty in later life is vital exhaustion. The construct of vital exhaustion was characterized by Appels et al. as a state of excessive fatigue and lack of energy accompanied by feelings of demoralization and irritability.\(^3\) Distinct from depression, vital exhaustion captures the effects of physical exhaustion, particularly fatigue and loss of vigor, as opposed to depressed mood.\(^4,5\) While first studied in the context of myocardial infarction, vital exhaustion has since been shown to be a precursor to several other poor health outcomes, such as stroke\(^6\), weight gain\(^7\), type 2 diabetes\(^8,9\), heart failure\(^9\), and coronary artery disease\(^10\), each of which may also contribute to frailty. Vital exhaustion is thought to be a result of overwork and chronic stress as well as mental fatigue due to coping with persistent stress.\(^5\) The deleterious physical effects of vital exhaustion may predispose individuals to frailty and/or be an early manifestation of subsequent frailty.

To our knowledge, no previous studies have studied the relationship between vital exhaustion and frailty. Studies have, however, established a prospective relationship between depression, which is highly correlated with vital exhaustion\(^5\), and increased frailty in later life.\(^11\) The goal of the current study is to test the hypothesis that elevated vital exhaustion measured in midlife independently predicts the onset of the frailty and pre-frailty phenotype two to three decades later in late-life using a large community sample of African American and Caucasian participants. In doing so, we will also examine the hypothesis that sex, race, and socioeconomic status modify this relationship. Given the differential rates of both vital exhaustion and fatigue across race, sex, and socioeconomic status\(^10,12-14\), it’s possible that the biological and non-biological factors underlying exhaustion in these groups may differ and so too may the relationship with frailty in later life.

5. **Main Hypothesis/Study Questions:**

**RQ1:** To investigate the association between midlife vital exhaustion (visit 2) and late-life pre-frailty and frailty (frailty indicated at either visit 5 or 6).

Hypothesis: Higher levels of vital exhaustion in midlife (visit 2) will be associated with increased risk of frailty and pre-frailty in late-life (frailty indicated at either visit 5 or 6). The association will be independent of comorbid chronic disease (measured by Charlson comorbidity index).

**RQ2:** To investigate heterogeneity of effects by participant sex, race, and socioeconomic status.
Hypothesis: The association will be stronger among females compared to males, among African Americans compared to Caucasians, and among those participants with low SES compared to high SES.

RQ3: To investigate the association between midlife vital exhaustion and the individual components of the frailty phenotype.
   Hypothesis: We hypothesize that midlife vital exhaustion will be most strongly associated with the following frailty components: exhaustion and low energy.

RQ4: To investigate the association between midlife vital exhaustion and change in frailty status from Visit 5 to 6.
   Hypothesis: Participants with higher levels of vital exhaustion in midlife will be more likely to transition to worse frailty status between visit 5 and 6.

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).

Inclusion/Exclusion Criteria:
Inclusion Criteria:
   1) Attended ARIC visit 5 and/or 6
   2) Available vital exhaustion data collected during visit 2

Exclusion Criteria:
   1) Participants missing information on all component characteristics defining vital exhaustion at visit 2
   2) Participants with documented clinical stroke before visit 5, as stroke may affect performance on functional measures of frailty.
   3) Participants with incomplete covariate data

Outcome Variables
Definition of frailty: All participants who attended visit 5 and/or 6 NCS have been categorized as *frail*, *pre-frail*, or *robust* based on the frailty phenotype definition operationalized by the Cardiovascular Health Study (CHS)\(^1\) and recently validated in the ARIC study.\(^15\) This definition of frailty is based on 5 components: exhaustion, slowness, low physical activity, and unintended weight loss. Participants are categorized as “frail” if they met 3 or more of the criteria listed below. Participants were categorized as “pre-frail” if they met 1 or 2 of the criteria listed below. Participants meeting none of the frailty criteria will be classified as “robust”.

1. **Exhaustion**: Participants who answered “some of the time” or “most of the time” to the following two questions on the Center for Epidemiological Study’s-Depression (CES-D) scale \(^16\) were classified as positive exhaustion: “I felt everything I did was an effort” and “I could not get ‘going’”.

2. **Slowness**: Walking speed was measured as the time needed to walk 4 m at a usual pace. Slow walking speed was defined as a time within the lowest 20\(^{th}\) percentile, adjusted for gender and height, as defined in CHS.
3. **Low Physical Activity**: Physical activity was measured using the modified Baecke questionnaire. Low physical activity was defined as reported physical activity in the lowest 20\(^{th}\) percentile stratified by gender.

4. **Weakness**: Grip strength in the participant’s preferred hand was measured at visit 5 using an adjustable, hydraulic grip strength dynamometer. Weakness was defined as grip strength in the lowest 20\(^{th}\) percentile, adjusting for gender and BMI according to established norms. Grip strength measures were not obtained for participants with bilateral surgery in hands or wrists in the previous 3 months.

5. **Weight Loss**: Weight loss was measured differently in V5 and V6. At V5, weight loss was defined as a 10\(^{\text{th}}\) weight loss from V4 to V5 (~15 years between visits) or a body mass index (BMI) at V5 less than 18.5kg/m\(^{2}\). At V6, weight loss measured as objective weight loss from V5 to V6 (~5 years between visits) OR self-reported unintentional weight loss; OR BMI <18.5. We will work with the frailty working group to determine the best method to handle this difference in weight loss assessments across visits.

**Exposure**

**Vital Exhaustion**: Vital exhaustion was assessed using the 21-item Maastricht Questionnaire at Visit 2 (questions listed in Appendix A). Responses to the questionnaire are coded as: Yes = 2; Don’t know = 1; No = 0 (questions 9 and 14 are reversed coded). Total score is calculated by summing across items (range 0 (no vital exhaustion) – 42 (high vital exhaustion)) with good internal consistency (Cronbach’s alpha = 0.89). Vital exhaustion can also be assessed as a binary indicator with vital exhaustion defined by scores that fall above the sample median of the Maastricht Questionnaire.\(^{17}\)

**Other Variables**

Demographic and study design covariate information was collected at Visit 1, including race-center, sex, education, and study center. Age, medical comorbidity (Charlson comorbidity index), cigarette smoking, and alcohol use (all measured at the same time vital exhaustion was measured (Visit 2)) will also be included as covariates. Socioeconomic status represented separately by education and income\(^{18,19}\) at Visit 1 will be included in effect modification analysis. We may also assess differences by neighborhood level measures of socioeconomic status. Sex and race will also be included in effect modification analysis (RQ2).

**Data Analysis**

RQ1: To examine the relationship between midlife vital exhaustion (exposure) and late-life frail and pre-frail status (outcome), we will use multinomial logistic regression to estimate odds ratios and 95\% confidence intervals of frail and pre-frail status (ref: robust). Vital exhaustion will be examined as continuous, categorical (categorized into quartiles (Q1 as reference category)), and binary (scores above the sample median of the Maastricht Questionnaire defined as “vital exhaustion”) variables to assess linear and nonlinear trends. We may also consider modeling frailty as a binary variable and using logistic regression to estimate odds of pre-frail/frail status (ref: robust). We will use the following stepwise regression models:

Model 1: Unadjusted analysis
Model 2: Adjusted for demographic variables (age, sex, race-center, education).
Model 3: Model 1 + medical comorbidity measured by the Charlson comorbidity score, cognition, cigarette smoking, and alcohol use)
We will determine the relevance of midlife vital exhaustion as a predictor of late-life frailty by calculating the AUC in the analyses described above. The vital exhaustion C statistic will be assessed both alone and in combination with relevant demographic and clinical factors. We will determine whether adding vital exhaustion to the predictive model significantly improves predictive power by evaluating the incremental change in the C statistic associated with midlife vital exhaustion.

We will conduct the primary analyses using only participants with available data. Our primary analyses will, as recommended by the ARIC analysis committee, account for participants who do not attend visits 5 or 6 using missing data methods, such as MICE, IPAW, and the Heckman correction as appropriate.

Because weight loss was measured differently at V5 and V6, we will work closely with the frailty working group to determine how to best define frailty at each visit. Possible ways to account for different weight loss measures in the construction of the frailty measure include 1) using the same weight loss measure across visits (e.g. BMI<18.5), 2) omitting the weight loss criteria for frailty and only using 4 criteria, 3) using a frailty index (based on Rockwood literature), and 4) using frailty variables at V5 and V6 with different weight loss definitions with acknowledgement of this limitation. We will conduct sensitivity analyses using these different definitions.

Sensitivity analysis will be conducted that excludes participants who may be frail at baseline identified as those who have four or more chronic conditions. Additionally, to address the possibility that associations between VE and late-life frailty are driven primarily by the exhaustion feature of frailty, we will exclude the exhaustion criteria from the definition of frailty and assess the association between VE and the non-exhaustion components of frailty. We will also include a category for death in the outcome variable to account for survival bias in a sensitivity analysis.

RQ2. We will add interaction terms to models used for RQ1 to evaluate effect modification by sex, race, and indicators of socioeconomic status (education and income). Separate interaction terms for each measure of socioeconomic status will be included.

RQ3. We will run 5 independent logistic regression models to assess the association between midlife vital exhaustion and the individual components of the frailty phenotype. We will use Poisson regression analyses (or negative binomial regression if assumptions for Poisson are not met) to determine how vital exhaustion relates to the total number (0-5) of frailty indicators.

RQ4. We will classify change in frailty status between Visits 5 and 6 as 1) No change 2) Improved frailty status 3) Worsened frailty status. We will use multinomial logistic regression to assess the odds of improved and worsened frailty status (ref: no change). We will also conduct sensitivity analyses using the definitions of frailty defined in RQ1 given the different methods of weight loss assessment.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __X__ 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  __X__ 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.cscc.unc.edu/ARIC/search.php  
____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)?
#2791 Association of Life’s simple 7 at mid-life with frailty in older adults  
#2671 Cardiovascular characterization of frailty in the elderly: The ARIC study  
#2465 Operationalizing frailty in the ARIC cohort  
#2303 Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study  
#3284 Association between hearing loss and frailty: A cross-sectional analysis from the Atherosclerosis Risk in Communities (ARIC) study  
#2930 Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study

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 at http://www.cscc.unc.edu/aric/forms/
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.
Understood

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.
Understood

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes __X__ No.
References


Appendix A: Maastricht Vital Exhaustion Questionnaire

The 21-item scale measured in ARIC includes questions marked with an asterisk items and the six items listed below.

Maastricht Vital Exhaustion Questionnaire

1. Do you often feel tired?
2. Do you often have difficulty falling asleep?
3. Do you wake up repeatedly during the night?
4. Have you felt less confident lately?
5. Do you sometimes have a feeling that you have got problems you cannot work out, in recent months?
6. Do you feel weak all over?
7. Have you been unable to stand loud noises lately?
8. Do you have a feeling that you haven’t been accomplishing much lately?
9. Do you have the feeling that you can’t cope with everyday problems as well as you used to?
10. Do you have a feeling that the future is becoming less and less certain?
11. Have you thought about deceased acquaintances or relatives more often lately?
12. Do you believe that you have come to a “dead end”?
13. Are you continuously worrying about your health?
14. Have demands been made on you lately that you could not cope with?
15. Do minor hassles easily irritate you in recent months?
16. Do you feel more listless recently than before?
17. Do you feel as if you are losing your self-control?
18. Do you have a feeling that nobody can help you with those problems deep down inside?
19. Have demands been made on you lately that you could only meet by making extra efforts?
20. I enjoy sex as much as ever. (no)
21. Have you experienced a feeling of hopelessness recently?
22. Do you often worry about your health?
23. Do you sometimes wonder whether you will still be alive tomorrow?
24. Does the feeling that you are a failure ever come upon you?
25. Do little things irritate you more lately than they used to do?
26. Do you feel you want to give up trying?
27. Are you becoming less satisfied with yourself?
28. Have you lately had a feeling, like “I do not achieve enough, I could achieve more if only I were healthier, not so weak, not so limp”?
29. Do you feel downcast?
30. Do you sometimes feel that your body is like a battery that is losing its power?
31. Do you sometimes have a feeling that you don’t know exactly where you stand?
32. Do you feel less capable of doing something useful nowadays.
33. Do you have a feeling that you family doesn’t understand you too well?
34. Would you want to be dead at times?
35. Have you felt strange bodily sensation lately?
36. Do you have the feeling that you don’t have what it takes anymore these days?
37. Can you bring yourself less and less to leave the house and go somewhere for a visit?

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Further items making up the 21 item Maastricht scale are:
(a) Does it take more time to grasp a difficult problem than it did a year ago?
(b) I feel fine
(c) Do you feel dejected?
(d) Do you feel like crying sometimes?
(e) Do you ever wake up with a feeling of exhaustion and fatigue?
(f) Do you have increasing difficulty on concentrating on a single subject for long?