1.a. Full Title: Muscle mass and strength and short-term risk of cardiovascular outcomes in community-dwelling older adults

b. Abbreviated Title (Length 26 characters): Muscle and prognosis in elderly

2. Writing Group:
   Writing group members: Kunihiro Matsushita, Shoshana H. Ballew, Priya Palta, Jennifer A. Schrack, Beverly Gwen Windham and Josef Coresh, others welcome

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

First author: Kunihiro Matsushita, MD, PhD
Address: 2024 E. Monument Street, Suite 2-600
          Baltimore, MD 21287
Phone: 443-287-8766      Fax: 443-683-8358
E-mail: kmatsus5@jhmi.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:
   Address:

3. Timeline:
   This ancillary study will basically use existing data, and we anticipate to complete the project in 1 year.

4. Rationale:
   Sarcopenia and cachexia are consequences of chronic diseases, such as advanced heart failure (HF). However, recent data demonstrate the possibility that lower muscle mass or strength may predate the development of cardiovascular diseases, particularly HF. There are several plausible mechanisms supporting this observation. Skeletal muscle is currently considered an endocrine organ, producing various proteins with potentially beneficial effects on the cardiovascular system. Accounting for ~40% of body weight in non-obese individuals, skeletal muscle is also a key organ for glucose utilization, and thus is an important determinant of insulin sensitivity and resistance. Lastly, skeletal muscle mass and strength may reflect an individual’s overall healthier lifestyle and higher level of physical activity. However, the impact of muscle mass and strength on adverse outcomes has been mainly evaluated for mortality, and thus data on cardiovascular events including non-fatal cases are sparse. Bioelectrical impedance data for
muscle mass and handgrip strength evaluations at ARIC visit 5 as well as adjudicated cardiovascular events will provide us with a unique opportunity to tackle this study question.

5. **Main Hypothesis/Study Questions:**
The main aim is to assess whether muscle mass and strength are associated with cardiovascular outcomes.

We hypothesize that muscle mass and strength will be inversely associated with future cardiovascular outcomes, particularly HF, in community-dwelling older adults.

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**
Analyses will include all black and white participants at visit 5 with data on bioelectrical impedance data and handgrip strength evaluation.

**Exclusions**
Race/ethnicity other than black or white
Participants with missing data on (1) bioelectrical impedance data (including participants with contraindications of bioelectrical impedance assessment such as a pacemaker, a defibrillator, or other internal electronic device) and (2) handgrip strength evaluation

**Exposure Variables at Visit 5**
- Muscle mass measures
  - Skeletal muscle mass (kg) will be estimated using the following formula validated against magnetic resonance imaging: \((\frac{\text{Height}^2}{\text{Impedance} \times 0.401} + (\text{gender} \times 3.825) + (\text{age} \times -0.071)) + 5.102\). Impedance was assessed during bioelectrical impedance analysis using the Tanita Body Composition Analyzer, TBF-300A, during visit 5
  - Lean body mass (kg) directly outputted from bioelectrical impedance analysis with the Tanita device
- Muscle strength measure
  - Handgrip: Grip strength in kilograms of force was assessed using Jamar Hydraulic Hand Dynamometer in participant’s preferred hand (usually the dominant)
- Other
  - Fat mass (kg): Since this is reciprocal of lean body mass, it is very likely that fat mass will show associations with cardiovascular outcomes opposite with lean body mass. However, the strength of association may be different.

**Traditional risk factors at Visit 5**
- Demographics: age, sex, race, education
- Medical history/comorbidities: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, stroke, or peripheral artery disease), hypercholesterolemia, hypertension, diabetes mellitus
- Laboratory/vital/lifestyle measures: cholesterol levels (total, HDL, LDL), triglycerides, glucose levels, kidney function and damage markers, heart rate, systolic blood pressure, diastolic blood pressure, ankle brachial index, body mass index, smoking and drinking status, physical activity
- Medications: antihypertensive medications, cholesterol-lowering medications, glucose lowering medication, and antiplatelet

**Cardiovascular outcomes:**
- Heart failure
- Coronary heart disease
- Stroke
- Peripheral artery disease
- Cardiovascular mortality
- All-cause mortality (this outcome will be also analyzed since cardiovascular disease is a leading cause of death in the US\textsuperscript{10}).

**Statistical Analyses**
We will first summarize baseline characteristics according to quartiles of muscle mass and strength. Also, we will evaluate correlations between those measures of muscle mass and strength. Subsequently, we will quantify the association of muscle mass and strength with adverse outcomes using Cox proportional hazards models. Exposures reflecting muscle mass and strength will be modeled as their quartiles and as continuous variables (1-SD as a linear term or spline terms, as appropriate). For grip strength, clinically relevant cutpoints will also be explored (<26 kg, 26-32 kg, and 32+ kg for men and <16 kg, 16–20 kg, and 20+ kg for women\textsuperscript{11}).

Subsequently, we will evaluate whether these muscle mass and strength measures can improve prediction statistics (calibration, discrimination, and reclassification) beyond traditional cardiovascular risk factors. We will repeat the analysis in several key demographic and clinical subgroups (e.g., presence/absence of history of cardiovascular disease [namely recurrent vs. incident cardiovascular events, respectively]) to evaluate the robustness of our findings. Since our analysis will be restricted to those participants who were able to attend visit 5, as a sensitivity analysis, we will conduct inverse probability attrition weighting to account for a possibility of selection bias.

As of the end of 2013, there were 237 HF cases (including both incident and recurrent cases) and 190 deaths after visit 5. Thus, for those events, we will be able to detect reasonable hazard ratio of 1.4-1.5 per 1-SD increment of muscle mass and strength with statistical power of 80%. We will also be able to repeat our analysis in spring/summer 2017 with updated outcomes through 2014 and higher statistical power.

**Limitations**
As stated in the prior section, we anticipate having adequate numbers of outcomes of interest for the overall analysis, statistical power can be an issue for some subgroup analyses. Both skeletal muscle mass and lean body mass are estimated values. Nonetheless, they have been shown to
associate with mortality in NHANES. As with all observational studies, we cannot rule out the possibility of residual confounding.

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.cscc.unc.edu/ARIC/search.php

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)?
To our knowledge, there are no ARIC proposals for muscle mass and strength measures and their associations with mortality and cardiovascular outcomes after Visit 5.

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* 2015.28)
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.
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.cscucc.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. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 ____ No.

References