ARIC Manuscript Proposal #2289

PC Reviewed: 1/14/14 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title:
Age at Menopause and Physical Function in Older Women: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Menopause and Physical Function

2. Writing Group:
Writing group members:
Ellen Demerath
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _EWD_ [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).
   Name: Ellen Demerath, PhD
3. **Timeline:**

4. **Rationale:**
Poor physical functioning is associated with institutionalization, hospitalization, and mortality. Identifying characteristics associated with poor physical functioning could contribute to prevention and management strategies that help older people to maintain their independence and their quality of life. Women consistently have lower levels of physical functioning than men in adulthood with evidence that physical functioning begins to decline at a faster rate among women than men from midlife onwards. The timing of the onset of more rapid decline in functioning among women coincides with the transition to menopause, during which time endogenous hormone production decreases. Changes in levels of hormones such as estrogen and progesterone may influence the decline in physical functioning, as these hormones are beneficial to muscle performance. Women who have menopause later may therefore have better subsequent physical functioning than women who have earlier menopause because of their longer period of exposure to endogenous hormones. Additional factors associated with surgical menopause may also influence physical functioning including events and conditions leading to surgical menopause, physical recovery from the surgery itself, or the premature alterations to hormone levels could result in lower physical functioning levels among women with surgical menopause compared to women who have undergone natural menopause.

A limited number of studies have examined the relationship of menopausal status with physical functioning and have had conflicting findings. Most have conducted cross-sectional analysis comparing physical function in pre-, peri- and post-menopausal women over a wide variation in age (e.g., Sowers et al., 2001; Sowers et al., 2008; Cooper et al., 2007; Kurina et al., 2004; Cheng et al., 2009; Kumari et al, 2005). Since pre-menopausal women in such studies also tend to be younger and generally healthier than the post-menopausal women, it has been difficult to confirm if menopausal timing, as distinct from chronological age at the time of measurement, is an independent risk factor for greater or more rapid physical dysfunction. Only one recent study has investigated, to our knowledge, whether age at menopause has a persistent association with physical functioning years later when all women are postmenopausal. Once all women within a population are postmenopausal, the potential confounding effects of age are not as great. That study (in 1765 women >60 years in NHANESIII) found that women with a surgical menopause had chair rise times that were an average of 4.4% slower than those of women with natural menopause (95% CI 0.56, 8.27). Women with natural menopause at age ≥ 55 years had an average walking speed 0.05 meters/second (95% CI 0.01, 0.10) faster than women with natural menopause at age < 45 years. Later ages at natural and surgical menopause were also related to lower self-reported functional limitation. Women with surgical menopause at age ≥ 55 years had odds of functional limitation 0.52 times (95% CI 0.29, 0.95) those of women with surgical menopause at age < 40 years, with similar patterns for natural menopause (Tom et al., 2012).
The ARIC study provides an opportunity to examine this question with greater depth and rigor given 1) the large number of objective measures of function and strength, 2) the examination of women at older ages when physical decline begins to become more common (65-90 years; up to 50 years after menopause), 3) ability to account for survival differences by timing and type of menopause, and 4) the relatively large sample of African American women in ARIC to allow for race differences in the relationship of menopausal type and timing to physical function to be tested.


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

**Primary Hypothesis:**
1. Later, as compared to earlier, age at natural menopause (continuous variable) is related to better physical function and strength at visit 5 using the NIA-recommended SPPB variables characterizing gait speed, chair rise speed, balance duration (and the summary score for this battery), and grip strength.

**Secondary hypotheses/analyses:**
2. Categorical menopause: There is a dose-response relationship between age at menopause (using established cutoff points of <45 years for early, 45-54 years for average, >=55 years for late) and physical function and strength.

3. Type of menopause: The relationship of age at menopause with physical function and strength at visit 5 differs by type of menopause (early surgical has stronger negative association with function than early natural).

4. Self-reported function: Because most existing studies use self-reported function as the outcome, we will test our primary hypothesis using self-reported physical ability outcomes (PAQ, visit 4) to allow for greater cross-study comparisons.

5. Effect modification/Protective effects: The association of age at menopause with physical function is modified by physical activity level; we hypothesize that the associations observed above will be attenuated among women with higher leisure time physical activity (continuous or active/inactive) using an interaction model (Age at menopause * Physical Activity term added). Other possible modifiers include race/ethnicity, and prevalent disease status.

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: Cross-Sectional Analysis

Exclusions: Male; Races other black or white;

Outcomes: (Physical Function and Strength)
   1. Physical Function: All SPPB vars (V5)
   2. Strength: Grip strength (V5)

Primary Predictors/Exposures:
   1. Age at menopause (continuous (Hypothesis 1) and categorical (Hyp. 2)
   2. Type of menopause (natural or surgical (Hyp 3)

Other covariates:
   Sociodemographic variables:
   1. Current age or time since menopause
   2. Race (use visit 1)
   3. Center (use visit 1)
   4. Education (use visit 1)
   5. Household income (use visit 1)
   6. MacArthur scales of relative SES (visit 5)

Potential confounders (unless noted, use VISIT CLOSEST TO AGE AT MENOPAUSE):
   1. Age at menarche (use visit 1)
2. Smoking history (packyears and current/former/never)
3. Alcohol use (current/former/never)
4. Use of hormone replacement (yes/no)
5. Duration of use of hormone replacement (years)
6. Marital status (NEVER vs EVER)
7. Number of children (0, 1, 2, >2)
8. Comorbidities (hypertension, diabetes, coronary heart disease, heart failure (V4-V5), stroke).

Data Analysis (summary):
Our primary strategy will use General Linear Models (GLM).

a. We will define categorical V5 Functional Group (FG) outcomes such as:
   
   \[ FG = \]
   
   1. Ideal: \( 10 \leq \text{SPPB} \)
   2. Intermediate: \( 6 \leq \text{SPPB} < 10 \)
   3. Poor: \( \text{SPPB} < 5 \)
   4. Dead

b. We will then use standard multinomial/ordinal GLMs with menopause variables to estimate relationship with V5 Functional Group status.
   
   Example:
   
   \[ g(FG_{ij}|b_i) = \beta_0 + \beta_1 \text{NatMeno}_i + \text{adjustors/interactions} \]

We will conduct analyses separately by race, then combine if estimates are similar.

Sample size Estimation (preliminary, visit 5 updated data not yet complete)
For primary analysis: All women with non-missing age at menopause and visit 5 SPPB variables

<table>
<thead>
<tr>
<th>Menopause Age</th>
<th>African American</th>
<th>White</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (&lt;45 years)</td>
<td>244</td>
<td>420</td>
<td>664</td>
</tr>
<tr>
<td>Not Early (&gt;=45 years)</td>
<td>348</td>
<td>1421</td>
<td>1769</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>592</strong></td>
<td><strong>1,841</strong></td>
<td><strong>2,433</strong></td>
</tr>
</tbody>
</table>

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  ___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.csc.c.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)?

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.

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.