1.a. Full Title:

Association between marital status and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Marital status and cognitive decline

2. Writing Group:

Writing group members:

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

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3. Timeline:
Data are currently available. Analysis will be performed within 6 months following receipt of the data.

4. **Rationale:**

Emerging evidence suggests that multiple risk factors including fewer years of education, cardiovascular diseases, and alcohol abuse are associated with cognitive decline in older population (Di Marco et. 2014). However, most studies focus mainly on physical characteristics and behaviors of individuals as opposed to interpersonal relationships and social networks. One important indicator is marital status, which could be an important risk factor of cognitive decline. Several studies have demonstrated that being single or widowed independently increases the risk of cognitive impairment compared to the married (Tsolaki et., 1997; Fan et., 2015). Yet these studies used either cross-sectional or retrospective study design and thus cannot address temporal issue.

A few prospective longitudinal studies have also explored the association, and all of them have discovered increased risk for dementia in people with single status (either widowed, divorced or never married) compared with the married group (Helmer et.,1999; Fratiglioni et.2000; van Gelder et. 2006; Hakansson et. 2009; Sundström et. 2013). However, among these studies, only one followed participants for more than 20 years. Moreover, most of the studies have a sample size of less than two thousand people. Thus evidence from prospective longitudinal studies with large samples of men and women are still needed in order to confirm the association between marital status and cognitive decline.

Even less is known about whether the association differs among subgroups defined by sex or social economic status (SES). Only one study showed that there is a gender difference in the association: Being single or widowed was associated with higher odds of cognitive impairment compared to being married in older Chinese men, but not women (Feng et.,2013). No research has ever investigated whether the association differs by SES status.

To address these research gaps described above, we propose to explore the association between marital status and cognitive decline, and effect modifiers, using longitudinal cognitive data from the ARIC study. This study will further our understanding about the influence of psychosocial factors such as marital status on cognitive function change.

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

1. To determine whether married participants on average have shallower cognitive decline in later life.
   
   *Hypothesis one: Those without partners (The divorced, separate, single, never married) at baseline (1987-1989) will have steeper rate of cognitive decline compared to the married.*

2. To determine whether the association of marital status and cognitive function decline differs by sex.
Hypothesis two: The association between marital status and cognitive decline is stronger among males than females.

3. To determine whether the association of marital status and cognitive function decline differs by SES.

Hypothesis three: The association between marital status and cognitive decline is stronger in a low SES group than in a high SES group.

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:
ARIC is a prospective cohort study with a sample size of 14623 community-dwelled older adults followed for up to 23 years. There are five follow up visits and cognitive function has been tested in three visits including visit 2 (1990-1992), visit 4 (1996-1998) and visit 5(2011-2013).

Inclusion/exclusion:
We will include all white and black ARIC participants who have completed three cognitive tests in at least one visit into our statistical model.

Outcome:
Three cognitive tests including digit symbol substitution (DSS) test, delayed word recall(DWR) and word fluency (WF) test were conducted at visit 2(1990-1992), visit 4 (1996-1998) and visit 5(2011-2013). The tests were administrated by trained staff in a standardized order during one session in a quiet room and same test version were used during all visits (Cerhan et., 1998). At visit 5, a more detailed and thorough cognitive battery of eleven tests was administered. We will use factor scores for general cognitive performance as well as specific domains of memory, language, and executive functioning computed by Gross and colleagues (2015):

- **Memory**: DWRT, DWRT-Recognition, Logical Memory I and II, Incidental Learning
- **Language**: WFT, Boston Naming, Animal Naming
- **Executive Function**: DSST, Trail Making Test Parts A and B, Stroop.

Exposure:
Marital status was collected at visit 1 (1987-1989) and visit 2 (1990-1992) based on data collected on the household enumeration from during interviewing. Marital status was not asked in visit 3 and visit 4. Respondent options included married, separated, never married, divorced, and widowed. We will categorize exposure into five groups based on the survey results and the married group will be treated as the reference group. We will also examine the marital status changes from visit 1 to visit 2 In a sensitivity analysis, we will exclude participants whose reported marital status changed after the visit 2 to examine whether marital change will influence the results. We will then decide whether treating it as a time fixed or time varying variable.
Potential confounders:
Information about potential confounders was collected at visit 1 including age (continuous variable), race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks), body mass index (<25 kg/m²; 25-<30 kg/m², ≥30 kg/m²), diabetes (yes or no), prevalent stroke (yes or no; defined by standardized criteria and physician adjudication), and prevalent coronary heart disease (yes or no; defined by standardized criteria and physician adjudication), cigarette history (never, former, current) drinking history (never, former, current).

Potential moderators:
Information about potential moderators including sex (male and female) and SES (3 classes: education <high school; high school, GED, vocational school; college, graduate or professional school, household income 3 classes: low (<$33,533), medium ($33,533-50,031) and high (≥$50,032) ) was collected at visit 1.

Data analysis:
We will examine the association between marital status and changes in cognitive test scores during three visits with multivariate mixed effects regression models. This model will account for the correlations between cognitive test scores measured in the same individual across different time points. In the model, we will include a random component to intercept to account for individual differences. The model will be adjusted for age, race, prevalent stroke, prevalent coronary heart disease, diabetes, BMI, alcohol use and smoking.

To assess whether the association between marital status and cognitive decline differs by sex and SES, we will add interaction terms between sex or SES and marital status in additional models. If there is any evidence for interactions, we will present stratified results.

To handle missing data and attrition in the cohort over 20 years, we plan to use multiple imputation by chained equations methodology (MICE) since it is a flexible method and an effective tool for imputing cognitive performance and improving assessment of cognitive decline (Rawlings et., 2016). We plan to impute 10-20 datasets based on the missing proportion. We will also perform sensitivity analysis to determine whether the data is missing at random (MAR) and account for attrition.

Methodologic limitations or challenges:
One of the major limitations is that we cannot investigate the relationship between marital status and incident dementia directly since the report of dementia relies heavily on proxies, who are usually spouses of participants, thus potentially biasing the results and MICE. Instead, we will investigate the cognitive function change measured by three cognitive tests and this may not be the best surrogate of dementia.
Another challenge is that some participants recruited into the cohort are couples, thus the marital status is dependent on each other. We are concerned that the stable unit treatment value assumption (SUTVA) assumption may be violated. So we will conduct a sensitivity analysis by excluding one of each pair to check whether the relationship between couples will influence the result. Moreover, since we will conduct stratified analysis by sex, coupling status at baseline is not a concern in this case.

There may also exist sample size issue in terms of exposure: We plan to divide variable of marriage status into five categories but there may be insufficient sample size for some categories such as never married or separate. If so, we will combine several categories into one category or treat marital status as binary variable (single and the married).

Finally, there are only 6351 people left in visit 5, the attrition rate is high (more than 50 percentage), which imposes challenges on data analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___X___ Yes  ___No

cognitive outcome

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)?
Andreea Rawlings proposal #2033: Cognitive domains in elderly blacks and whites in the Atherosclerosis Risk in Communities Neurocognitive Study.

Alden Gross proposal #2215: Application of latent variable methods to the study of cognitive decline when tests change over time.

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
   __X__ A. primarily the result of an ancillary study (list number* __ARIC NCS 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 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.

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 ____ No.

References:


