ARIC Manuscript Proposal #2651

PC Reviewed: 10/13/15   **Status:** <u>A</u>   **Priority:** <u>2</u>
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: The association between parity and subsequent cardiovascular disease in women: The Atherosclerosis Risk in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters): **Parity and CVD**

2. Writing Group:
     Writing group members: Clare Oliver-Williams, Catherine Vladutiu, Laura Loehr, Alison Stuebe, Wayne Rosamond (has been invited, but has not yet approved this proposal)

I, the first author, confirm that all the co-authors have given their approval for this manuscript proposal. CTOW **[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).

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3. Timeline: 12 months to the final draft of the manuscript

4. Rationale:

Cardiovascular disease (CVD) is the leading cause of death in women in every major developed country and most emerging economies (Gholizadeh and Davidson 2008). One in three female adults in the U.S. has some form of cardiovascular disease; 6.6 million U.S. women have coronary heart disease (CHD) and 3.8 million females are stroke survivors (Go et al. 2013).

Pregnancy, even an uncomplicated pregnancy, places enormous stress on a woman's body. Physiological changes occurring during pregnancy include weight gain, accumulation of abdominal fat, higher lipid levels, increased insulin resistance, and structural cardiac changes (Fåhraeus, Larsson-Cohn, and Wallentin 1985; Parikh et al. 2012; Sadaniantz, Saint Laurent, and Parisi 1996). Although most changes that occur during a healthy pregnancy are temporary, pregnancy affects established CVD risk factors, and thus may have long-term implications for cardiovascular health (World Health Organisation 2015). Recognizing that the unique cardiovascular stress that occurs during pregnancy can be used to improve CVD risk prediction, the 2011 American Heart Association guidelines incorporated obstetric complications in the assessment of CVD risk in women (Mosca et al. 2011), and made a call for further research into CVD risk in relation to pregnancy, which has been reiterated subsequently (Rich-Edwards et al. 2014; Roberts and Catov 2012).

Previous studies have assessed the relationship between parity and several cardiovascular outcomes (Jacobsen et al. 2011; Jung et al. 2010; Lv et al. 2015; Parikh et al. 2010), including CVD (Ness et al. 1993), CHD (Lawlor et al. 2003), and stroke outcomes (Gaist et al. 2004; Koski-Rahikkala et al. 2006). However, the results of these studies have been inconclusive as to the shape and presence of the association, with some studies noting a J-shaped relationship (Lawlor et al. 2003; Parikh et al. 2010; Steenland, Lally, and Thun 1996) with the nadir of risk for primiparous (Jung et al. 2010) or nulliparous (Ness et al. 1993) women, whereas other studies found the lowest risk among multiparous women, when compared to nulliparous women (Lv et al. 2015; Parikh et al. 2010), and other studies found no relationship (Jacobsen et al. 2011; Stöckl et al. 2013).

Few studies have evaluated multiple cardiovascular outcomes within the same population, making it difficult to confirm the relative size and shape of the relationship across multiple endpoints. One of the largest studies conducted, using Swedish registries, assessed CHD, stroke, heart failure and total CVD (Parikh et al. 2010). However, this study was limited by an inability to differentiate the nulliparous group into those who chose not to have children, and those who became pregnant but miscarried. Additionally, it did not adjust for body mass index (BMI) under the premise that it may be a mediator not confounder of the association, as measures were taken after the births. Furthermore, only hospitalized cases of CVD could be included, raising the question of whether the association is as strong in milder cases where individuals are treated as outpatients. Other studies have been limited by similar factors (Gallagher et al. 2011; Jacobs et al. 2012; Jacobsen et al. 2011).

Many of these issues can be addressed using data from ARIC. First, there is information available on self-reported weight at age 25, which is close to the mean age at first birth in ARIC (mean: 22, SD: 4.2). These data will enable assessment of the association with three options for adjustment of BMI: 1) without adjustment for BMI, 2) with adjustment for BMI at baseline, and, 3) adjustment for BMI at the time of first birth or prior to birth. Second, ARIC has data on both hospitalized CVD outcomes and silent myocardial infarction, angina pectoris and intermittent claudication. The latter three outcomes, pertinent to cardiovascular health in women, will allow assessment and comparison of the magnitude of the association of hospitalized and non-hospitalized CVD outcomes. Third, the heterogeneous nulliparous group can be separated into those individuals who had been pregnant but did not have a live birth and those who have never been pregnant, allowing the assessment of the potential impact of this differentiation on CVD risk. Finally, the ARIC study has detailed information on lipids, allowing for further assessment of the potential confounding or mediating role of these relevant biomarkers. To the authors' knowledge, these variables have not been assessed as covariates in previous studies.

In summary, further clarity on the relationship between parity and CVD is needed. The assessment of the relationship within ARIC will add to the body of evidence, while allowing the assessment of several clinically relevant CVD outcomes.

5. **Main Hypothesis/Study Questions**:
1. Is there an association between parity and overall cardiovascular disease?

Hypothesis: Nulliparous (no prior live birth) and multiparous (more than 1 prior live birth) women will have a higher incidence of CVD as compared to primiparous (1 prior live birth) women, with a J-shaped association expected. This hypothesis is based on the assumption that nulliparous women in the study population include those with a history of infertility as well as those who did not intend to have children. Conditions that contribute to infertility may be associated with CVD risk factors, thus increasing the incidence of CVD among nulliparous women. In an attempt to differentiate between the heterogeneous group of nulliparous women, we will assess separately those who have been pregnant but did not have a live born child and those who have never been pregnant. Among multiparous women, the cumulative effects of physiologic adaptations and complications across successive pregnancies likely increase the incidence of CVD.

2. Is there an association between parity and clinical subtypes of CVD (i.e., stroke, coronary heart disease, myocardial infarction and all-cause mortality)?

Hypothesis: Same as above, but with individual CVD outcomes.

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 population/inclusion/exclusion: This study will include a cohort of approximately 8000 women, ages 45-64 years, who participated in the ARIC study baseline visit in 1987-1988. Follow-up for CVD events will be through the most recent year available, currently 2011. Men will be excluded from the analysis, as will any women with missing exposure or outcome information.

Variables:

Exposure: Parity (defined as the number of prior live-born children).

Outcomes: Incident cardiovascular events of myocardial infarction (MI), CHD (defined as MI as well as women who have had coronary artery bypass graft, or angioplasty/atherectomy procedures), stroke (both ischemic and hemorrhagic stroke and transient ischemic attack (TIA)), composite cardiovascular disease (combining stroke and CHD), cardiovascular mortality, and all-cause mortality, angina pectoris, intermittent claudication

Additional variables required for analysis are listed below: Age at first pregnancy, Age at first birth, Age at menarche, Age at menopause, Age at natural menopause, Age at oophorectomy, Age at surgical menopause, Alcohol consumption, BMI, Breast feeding duration, Date of birth, Date of death, Diastolic blood pressure, Educational level, Ever been pregnant, Ever given birth, Exposure: number of live born children, Fasting blood glucose, HbA1c, HDL-c, Height, High blood cholesterol, Hip girth, History of MI, HRT use (ever/current), Hypertension, Hypertension medications, Hysterectomy, Income, LDL-c, Marital status, Medical insurance, Diabetes medication, Menopausal status, Natural/surgical menopause, Number of pregnancies, OC use (ever), Occupation, Oophorectomy, Race, Systolic blood pressure, Self-reported diabetes, Self-reported stroke, Sex, Smoking (cigars), Smoking (cigs), Smoking (pipe), Total cholesterol, Triglycerides, Waist girth, Weight, Weight at age 25, WHR, Year of recruitment, ID.

Statistical analyses:
Baseline characteristics will be summarized by parity categorized as 0, 1, 2, 3, 4 and 5+ births. Continuous variables will be presented by median and interquartile range (IQR) and compared using Kruskal-Wallis tests, while categorical variables will be presented as number and percentages, and compared using χ^2 tests. Risk of CVD events will be modeled using multivariable Cox proportional hazards regression models. Maternal age will be the time scale. Patients who died of other causes or were lost to follow-up will be censored. The proportional hazards assumption will be tested using the test of Grambsch and Thearneu (Grambsch and Therneau 1994). Parity will be assessed separately as a continuous and categorical variable. The shape of the associations will be displayed graphically and confidence intervals will be calculated with floating absolute risks. Risk will be assessed, with the results meta-analyzed and any heterogeneity quantified using the Cochrane χ^2 statistic and the I^2 statistic. Stratified analyses will assess variations in the associations by ethnicity, socioeconomic status and time, due to the decreasing parity

and breastfeeding rates, which may reset maternal metabolism post-pregnancy, over time, coupled with the greater CVD risk with age, as well as variation in parity and breastfeeding with socioeconomic status, which is also strongly related to CVD risk.

Missing data: Variables, with the exception of the exposure or outcome, that are missing 10% or more will be imputed using multiple imputation by chained equations and stratified by center. The number of imputations generated will reflect the proportion of records with missing data.

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)?**
MS#1170: Reproductive history, hormone replacement, and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology.
MS#991: Parity and Risk of Type 2 Diabetes: The Atherosclerosis Risk in Communities study

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* _____)
    ___ 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 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.