ARIC Manuscript Proposal #2525

PC Reviewed: 4/14/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Association of Age at Menopause and Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Age at menopause and heart failure

2. Writing Group:
Writing group members: Duke Appiah, Pamela J. Schreiner, Ellen Demerath, Laura Loehr, Patty Chang, Aaron R. Folsom

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

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3. Timeline: A draft will be sent to the coauthors by the end of July 2015 and a final draft will be submitted to the P&P Committee by September 2015

4. Rationale:

The association between menopause and incident cardiovascular disease (CVD) is controversial and the underlying mechanisms for these conflicting results are not well understood. Numerous reports document elevated risk of CVD in women with early natural or surgical menopause (before age 45 years) which is attributed to loss of endogenous estrogen (1, 2). Women with early menopause have a shorter duration of exposure to endogenous estrogens than women who reach menopause at a later age. Estrogen has been reported to have a protective effect on coronary vasculature (3, 4) although trials of hormone therapy in recently menopausal women appear to cast doubt on estrogens' cardio-protective role in CVD development among postmenopausal women (5, 6). Adverse CVD risk factor levels are associated with early onset of natural menopause (7). Therefore the reported associations of early menopause with CVD may be due to unfavorable CVD risk profiles found in such women.

A few short-term studies with small samples suggest that early onset of menopause is related to greater likelihood of ventricular dysfunction (8-11). While the presence of ventricular dysfunction (systolic or diastolic) raises the risk for overt heart failure (12, 13), investigations of the relationship between early menopause and incident heart failure are limited. Heart failure has tremendous effects on women's cardiovascular health and quality of life. Approximately 2.5 million women in the United States are diagnosed with heart failure and of the 522,000 hospitalizations attributable to heart failure each year, 52% occur in women (14). Heart failure is responsible for more than a third of all CVD deaths in women even though women have better prognosis than men (14). Therefore clarifying how early age at menopause may influence heart failure risk is critical.

Two recent studies from the Swedish Mammography Cohort (15) and the Multi-Ethnic Study of Atherosclerosis (16) report a 40% and 66% greater risk of heart failure in women with early menopause. The former study only assessed a homogeneous cohort of white naturally menopausal women, which limits the generalization of the findings to other races. The latter study was small and failed to distinguish between types of menopause, which may have led to misclassification as women with hysterectomy and ovarian conservation were considered to have surgical menopause. Therefore, further evidence is needed to clarify the association. The objective of the proposed study is to assess the independent association of age at menopause with incident heart failure in a biracial cohort of postmenopausal women enrolled in Atherosclerosis Risk in Communities Study.

5. Main Hypothesis/Study Questions:

Early age at menopause is associated with greater risk of incident heart failure.

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).

Design: cohort beginning at ARIC visit 1

Exclusions:

The main analysis will be restricted to postmenopausal women at visit 1 and those who reach menopause at visits 2 and 4. For women who enter the analytic cohort during follow-up, their

baseline will be set to the visit at which they reported undergoing menopause. Participants with prevalent heart failure (and those missing data to determine prevalent heart failure) or coronary heart disease (CHD) at baseline (visit 1) will be excluded. Prevalent heart failure will be defined as self-reported use of heart failure medication in the previous two weeks or a stage 3 heart failure based on the Gothenburg criteria.

Predictor variable

Age at menopause defined as (17)

(a) natural menopause : age at final menstrual period which is not preceded by hysterectomy.
(b) hysterectomy and bilateral oophorectomy: age at menstrual cessation due to bilateral oophorectomy)
(c) hysterectomy with at least one ovary conserved:
    i. age at which a woman began using hormone therapy or first had vasomotor symptoms (i.e., hot flashes, night sweats)
    ii. if hysterectomy at age 50 years or older but no use of hormone therapy or symptoms, the age at menopause will be defined as the age when the hysterectomy was performed. If this algorithm defined an age at menopause as older than 60 years, it will be recoded as 60 years.

Age at menopause will be categorized into several groups, with early menopause defined as occurring before age 45 years.

Outcome
Incident heart failure will be defined as first hospitalization with an ICD-9/10 discharge code of 428.x/150 or deaths with heart failure as the underlying cause occurring after baseline through to December 31, 2012.

Covariates (Visits 1 and other indicated visits)

Demographic variables: age, race, ARIC field center, educational level (years of education) and medical insurance status.

Anthropometric measures: baseline and follow-up (visit 2 to 5) waist circumference and body mass index.

Reproductive factors: age at menarche, parity, hysterectomy status and hormone therapy use.

Health behavioral/lifestyle factors: smoking status (never, current, former) and pack years, physical activity (Baecke PA scores) and alcohol use.

Health history and conditions: baseline and follow-up (visit 2 to 5) systolic blood pressure and anti-hypertensive medication use, diabetes, lipid-lowering medication use.

Lipids: baseline total and HDL cholesterol, serum creatinine and estimated glomerular filtration rate.

Statistical analysis

Descriptive statistics will be calculated to describe the study participants in the cohort component of the ARIC study according to age at menopause (< 45, 46-49, 50-54 and ≥55 years). Categorical variables will be compared between groups using chi-square tests while comparisons of continuous measures will be tested using analysis of variance (ANOVA). In instances in which continuous measures are skewed, results will be normalized by Log transformation. When normality is still not achieved by this procedure we would employ Kruskal-Wallis test, a non-parametric test or we may categorize such variables. In the analysis of time to event, incidence rates for heart failure by age at menopause group will be reported with Kaplan-Meier curves produced. Log-Rank tests will be used to test for differences in survival curves. Cox regression models will be employed to assess the association of age at menopause (modelled as a continuous and categorized variable) with incident heart failure in crude and adjusted models. Adjustments will be made for the following confounders (age, race, BMI, center, smoking status and amount, systolic blood pressure, antihypertensive, lipid-lowering medication use, physical activity, alcohol use, age at menarche, parity, hormone therapy, diabetes, estimated glomerular filtration rate, total and HDL cholesterol). Formal interaction tests of age at menopause and type of menopause (natural, hysterectomy with ovarian conservation or hysterectomy with bilateral oophorectomy) as well as conventional CVD risk factors will be conducted. We will also perform analyses stratified by race. Due to the long follow-up duration, we will also model BMI, systolic blood pressure and antihypertensive medication use as time-dependent covariates in secondary analyses. To assess if the observed association is mediated by CHD, we will further adjust for interim CHD defined as CHD which occurs before heart failure during follow-up. In other explorative analyses, we will consider all non-heart failure deaths as competing risk events. The proportional hazards assumption will be tested using cumulative sums of Martingale-based residuals methods. To explore the possibility of nonlinear and dose-response relationships between age at menopause and heart failure, restricted cubic and natural splines will be used with knots set at the quartiles of age at menopause. A two-tailed probability value less than 0.05 will be considered statistically significant in all analyses. Reproductive lifespan (age at menopause minus age at menarche) although highly correlated with age at menopause has been suggested to be a better measure for quantifying lifetime endogenous estrogen exposure than age at menopause (18). Therefore, we will explore the association of reproductive lifespan with incident heart failure using the methods described above.

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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)?

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.