1.a. Full Title: Is age at natural menopause associated with cardiovascular events independent of antecedent cardiovascular health? The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Natural menopause and CVD

2. Writing Group:
Writing group members: Duke Appiah, Imo Ebong, Melissa Wellons, Pamela Schreiner, Nora Franceschini, Ellen Demerath

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __DA___ [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 April 2019 and a final draft will be submitted to the P&P Committee by July 2019

4. Rationale:
The association between menopause and incident cardiovascular disease (CVD) is controversial [1-5]. Menopause has been reported to alter women’s exposure to endogenous ovarian hormones and has been suggested to increase CVD risk [4]. Most prior studies assessing the risk of age at menopause with incident CVD events only measured CVD risk factors many years after menopause, without assessment of antecedent CVD risk factor levels. This limits the determination of the association’s temporality as unfavorable CVD risk profiles are known to be associated with menstrual cessation [3, 6-8].

A growing body of research from the Coronary Artery Risk Development in Young Adults (CARDIA) Study as well as the study of Women's Health across the Nation (SWAN) have shown that after accounting for the effect of pre-menopausal CVD risk factors, there are no differences in CVD risk factors levels or intermediary CVD outcomes namely left ventricular structure and function in the postmenopausal period regardless of the age of final menstrual period [7-10]. However, it is unknown if this same effect will translate to incident CVD endpoints.

The objective of the proposed study is to investigate the association of age at natural menopause and reproductive lifespan (age at natural menopause minus age at menarche) with incident CVD outcomes independent of antecedent CVD risk factors in the biracial cohort of women enrolled in Atherosclerosis Risk in Communities Study. The ARIC study is unique to address this association as 3,508 (40%) of the 8710 women enrolled at baseline transitioned to menopause during ARIC visit 2 to 4 and therefore had extensive CVD risk factor assessments prior to the onset of menopause as well as a long follow-up periods to allow for the assessment of incident CVD events.

A limitation of this proposed study is that women who reached natural menopause before age 45 years of whom some studies have identified to have a high risk for CVD events will be excluded by design. This limitation, however, is also a strength since women with primary ovarian insufficiency who may likely be driving the reported association of early menopause with CVD events due to underlying pathological and genetic disorders [11, 12] will be excluded from the proposed study. Ultimately, the findings of the proposed study will help clarify whether the elevated risk of CVD events reported in prior studies among women with early natural menopause are primarily due to either endogenous estrogen deficiency, biological aging or cardiovascular disease risk factors occurring in the premenopausal years.

5. Main Hypothesis/Study Questions:

Is age at natural menopause associated with cardiovascular events independent of antecedent cardiovascular risk factors?

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 analysis will be restricted to women who were not menopausal or have undergone hysterectomy at ARIC visit 1 but reach natural menopause at visits 2 through to 4. For these women who enter the analytic cohort during follow-up, their baseline (antecedent risk factors) will be set to the prior visit(s) at which they reported not being menopausal. Participants with prevalent coronary heart disease (CHD) and stroke at the time of entry into the analytic cohort and those with missing age at natural menopause or menstrual cessation due to radiation or chemotherapy will all be excluded.

Predictor variable

Age at menopause defined as the age at final menstrual period which is not preceded by hysterectomy.

Outcome Variables

Incident events occurring after visit 1 through to December 31, 2017.

1. Coronary heart disease (CHD) as defined by a definite or probable diagnosis of myocardial infarction, definite fatal CHD and/or coronary revascularization (CABG or PTCA).
2. Stroke (ischemic and hemorrhagic)
3. Total CVD as defined by the above plus other cardiovascular-related deaths.

Covariates (Visits 1 to 4)

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

Anthropometric measures: waist circumference and body mass index.

Reproductive factors: age at menarche, parity, hysterectomy status, oophorectomy 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: systolic blood pressure and anti-hypertensive medication use, diabetes, lipid-lowering medication use.

Lipids: total and HDL cholesterol, total fibrinogen, and fasting glucose.

Statistical analysis
Descriptive statistics will be calculated to describe the study participants in the cohort component of the ARIC study according to age at natural menopause (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 CHD, stroke and total CVD by age at natural 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 natural menopause (modelled as a continuous and categorized variable) with incident CHD, stroke and total CVD in crude and adjusted models. Because CVD events rates increase with advancing biological age, attained age in years will be used as the time scale for all time-to-event analyses. Furthermore, because of the variable lengths of follow-up for participants, models that account for left truncation of the data as a result of the staggered entry will be used. Adjustments will be made for the following antecedent CVD risk factors occurring at the prior visit at which a woman was premenopausal (race, BMI, ARIC center, smoking status, systolic blood pressure, antihypertensive, lipid-lowering medication use, physical activity, alcohol use, age at menarche, parity, hormone therapy, diabetes, total fibrinogen, total cholesterol and HDL cholesterol). Formal interaction tests of age at menopause and conventional CVD risk factors (smoking, BMI, hormone therapy use, etc.) 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. 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 natural menopause and CHD, stroke and total CVD, restricted cubic splines will be used with knots set at the quartiles of age at natural menopause. A two-tailed probability value less than 0.05 will be considered statistically significant in all analyses. Reproductive lifespan (age at natural 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 [13]. Therefore, we will evaluate the association of reproductive lifespan with incident CHD, stroke and total CVD using the methods described above. Finally, exploratory analyses of the association of age at natural menopause with other incident CVD-specific outcomes namely heart failure (total events as well as heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved ejection fraction (HFpEF), peripheral artery disease and venous thromboembolism while accounting for antecedent CVD risk factors will be conducted. For such analyses, all the corresponding prevalent CVD cases will be excluded.

REFERENCE


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/mantrack/maintain/search/dtSearch.html

____ ✓__ 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 #2525, "The Association of Age at Menopause and Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study" [PMID: 27468929]

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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.