1.a. Full Title: Parental history of cardiovascular disease and the risk of incident coronary heart disease and stroke in women with and without bilateral oophorectomy: the Atherosclerosis Risk in Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): CVD in women by BSO status.

2. Writing Group:
   Writing group members:
   Appiah D. PhD MPH, Schreiner PJ, PhD MS, Folsom AR, MD MPH, Winters SJ, MD, Hornung CA, PhD MPH.

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]

   First author: Duke Appiah
   Address: Division of Epidemiology and Community health, University of Minnesota, 1300 S 2nd St. Suite 300 Minneapolis MN 55454
   Phone: 612 626 5458    Fax: 612-624-0315
   E-mail: dappiah@umn.edu

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: Aaron R. Folsom, MD, MPH
  Address: Division of Epidemiology and Community health, University of Minnesota, 1300 S 2nd St. Suite 300 Minneapolis MN 55454
  Phone: 612-624-8862    Fax: 612-624-0315
  E-mail: folso001@umn.edu

3. Timeline: A draft will be submitted to the coauthors by the end of December 2014. A final draft will be submitted to the P&P Committee by the end of March 2015

4. Rationale:

   Whether there is an association of bilateral oophorectomy (BSO) with incident cardiovascular disease outcomes is controversial (1-5), and the underlying
mechanisms for these conflicting results are not well understood. BSO, the surgical removal of the ovaries, is commonly performed electively in conjunction with hysterectomy for women with uterine fibroid tumors, endometriosis, uterine prolapse, or chronic anovulation with dysfunctional uterine bleeding. When performed at an early age, BSO alters a woman’s exposure to endogenous ovarian hormones which has been suggested to increase CVD risk (3, 4). However, other studies report no elevated CVD risk among women with early BSO without exogenous hormone therapy use compared to hysterectomized women with ovarian conservation or naturally menopausal women (2, 5).

Several CVD risk factors such as insulin resistance, general and abdominal obesity, low HDL and hypertension (6-9) have been reported to occur more often than expected in women who undergo BSO, and our previous investigations suggest that women who undergo BSO at an early age tend to have a family history of premature CVD (10). These associations suggest that CVD risk with BSO may in part reflect a genetic susceptibility to CVD.

Numerous epidemiologic studies have observed familial aggregation of traditional CVD risk factors including hypertension, dyslipidemia, diabetes, cigarette smoking, and obesity, which point to a genetic basis for these conditions as well as shared social and physical environmental characteristics (11-13). Parental history of CVD is often considered a surrogate measure of genetic susceptibility to CVD events (11-15). However, it has the unique advantage of also capturing other biochemical and behavioral components which predisposes individuals to elevated CVD risk, and is known to predict incident CVD events independent of traditional CVD risk factors (11-16). Despite a positive parental history of CVD having the ability to influence CVD risk factors which, in turn, may be an effect modifier of the indications for surgical menopause and CVD events, investigations into its impact on the association of BSO with incident CVD are lacking.

The objectives of the proposed study is to assess the independent and joint associations of parental history of CVD, either coronary heart disease or stroke and BSO with incident CVD events, and also to evaluate the relationship of parental history of premature CVD with the occurrence of BSO at an early age.

5. Main Hypothesis/Study Questions:

1. We hypothesize that among all women stratified by BSO status, those with a positive parental history of CVD will have elevated incidence of CVD compared to those without such parental history. We further hypothesize a positive interaction between BSO and parental history of CVD.

2. A parental history of premature CVD as defined by paternal history of CVD before age 55 years or maternal history of CVD before age 65 years will be positively associated with the occurrence of BSO at an early age (< 46 years).
3. BSO performed at an early age (< 46 years) will predispose women to a greater risk of CVD than BSO after age 50 years (the average age at natural menopause) independent of hormone therapy use.

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).

Exclusions

Women with prevalent CHD, heart failure, or stroke at baseline will be excluded. Additionally, to reduce the occurrence of misclassification bias, participants who reported not knowing the family history of at least one parent will be excluded, as well as women with incident BSO after baseline.

Predictor variables

Baseline measures of family history of CVD as defined by a parental history of coronary heart disease (CHD) or stroke.

Incident outcome variables

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

Covariates

Demographic variables: age at baseline, race, household income, educational level (years of education), and medical insurance status.

Anthropometric measures: baseline weight, waist circumference and body mass index.

Reproductive factors: age at menarche, age at menopause, parity, hysterectomy status, oophorectomy status, estrogen alone hormone therapy use, and estrogen plus progestin hormone therapy use.

Health behavioral/lifestyle factors: smoking status (never, current, former or pack years/years quit smoking) and physical activity (Baecke PA scores).
Health history and conditions: baseline systolic blood pressure, anti-hypertensive medication use, diabetes and lipid-lowering medication use.

Lipids: baseline HDL and LDL cholesterol and triglycerides

**Statistical analysis**

Descriptive statistics will be calculated to describe the study participants in the cohort component of the ARIC study according to parental history of CVD and bilateral oophorectomy status. Categorical variables will be compared between groups using chi-square test while quantitative comparisons will be tested using analysis of variance (ANOVA). In instances in which quantitative measures are skewed, results will be normalized by Log transformation and when normality is still not achieved by this procedure we would employ Kruskal-Wallis test, a non-parametric test. In the analysis of time to event, frequencies of incident CVD will be reported with Kaplan-Meier curves produced and Log-Rank test used to test for differences in survival curves. To test hypothesis 1, we will use Cox regression models to assess the effects of parental history of CVD and BSO status with incident CVD. Formal interaction test of parental history of CVD and BSO status will be conducted as well. Four models with progressive degrees of adjustments will be employed in all analysis. Model 1 will adjusted for demographic factors. Model 2 will add reproductive factors to model 1 while model 3 will further adjust for anthropometric measures and health behavioral/lifestyle factors and health conditions. Finally model 4 will adjust for plasma lipid levels. To test hypothesis 2, a logistic regression model will be used to estimate the odds of BSO before 46 years given a positive parental history of premature CVD with the same progressive degrees of adjustments mentioned above. Finally, to address hypothesis 3, we will employ proportional hazards models to assess the risk of incident CVD with age at BSO (<46, 46-50, >50 years) with women without BSO as referent. Sensitivity analyses limited to women with a history of hysterectomy at baseline will be performed with women having both hysterectomy and BSO compared to hysterectomised women with ovarian conservation (referent). Based on an estimated accrual period of 3 years and an additional follow-up of approximately 21 years, and given that there are 456 women with BSO and a positive parental history of CVD (exposed group) and 904 women with BSO without parental history of CVD (unexposed), we will be able to detect true hazard ratios (relative risks) of failure for unexposed subjects relative to exposed subjects 0.809 or 1.256 with probability (power) 0.80. The Type I error probability associated with this test of the null hypothesis that the exposed and unexposed survival curves are equal is 0.05.

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.csc.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.csc.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

REFERENCE