

**ARIC Manuscript Proposal #3587 (revised)**

**PC Reviewed:** 6/9/20

**Status:** \_\_\_\_\_

**Priority:** 2

**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_

**Priority:** \_\_\_\_\_

**1a. Full Title:** Early menopause, body fat distribution and the risk of incident heart failure in post-menopause women of the ARIC study

**b. Abbreviated Title:** Early menopause, body fat distribution and heart failure

**2. Writing Group:**

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

I.A.E

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**3. Timeline:** 12 – 18 months

**4. Rationale:**

Menopause has emerged as a female specific risk factor for cardiovascular diseases such as heart failure. Early menopause which is defined as the occurrence of menopause before forty-five years of age has been associated with heart failure in prior studies.<sup>1-3</sup> Although speculations exist, the exact mechanisms that link early menopause with heart failure are currently unknown. Heart failure affects approximately 3.2 million American women.<sup>4</sup> Approximately 10% of women experience natural menopause before 45 years of age.<sup>2</sup> It is crucial to understand the associations between menopause and heart failure in order better target high risk women for aggressive risk factor modification and close surveillance.

Body fat deposition increases during the menopausal transition and continues into the post-menopause period.<sup>5-7</sup> Generalized and abdominal obesity have been associated with heart failure incidence in multiple studies.<sup>8-12</sup> The relationship between obesity and incident heart failure is related to hemodynamic and anatomic cardiac changes, hormonal and metabolic changes, inflammation and comorbidities resulting from excess body fat.<sup>13-15</sup> Menopause is also associated with hormonal changes, metabolic derangements, inflammation and lipid abnormalities which are all risk factors for developing heart failure.<sup>1,16</sup>

Preserved ejection fraction heart failure occurs more commonly in women than men<sup>17,18</sup> and may be related to body fat distribution changes with early menopause. We will evaluate the effects of body fat distribution on the relationship between early menopause (and menopause age) with incident heart failure. We will also explore the relationships of early menopause (and menopause age) according to heart failure subtypes. The Atherosclerosis Risk in Communities (ARIC) study is a multicenter prospective biracial cohort that enrolled and examined 15,792 participants (8710 women), aged 45 to 64 years at baseline (1987-1989). At follow up visit 5 (2011 to 2013), all ARIC women were postmenopausal and aged between 67 to 90 years. The ARIC cohort is suitable to perform this study because there is detailed reproductive history on all ARIC women at visit 4. The ARIC reproductive history questionnaire collected information on menstrual history, causes of menopause, age at menopause, gynecological surgeries such as hysterectomy and oophorectomy and use of hormone replacement therapy. At each ARIC Visit, a woman was classified as having reached natural menopause if they had failed to experience a menstrual period in the prior two years before the visit date and surgical menopause if they had bilateral oophorectomy performed before 55 years of age or the occurrence of natural menopause. The

ARIC postmenopausal cohort consists of women with both natural and surgical menopause. Data on prevalent heart failure is available at visit 5. Heart failure events in the ARIC study have been fully adjudicated after visit 5 and there is information on preserved and reduced ejection fraction heart failure. There are 138 heart failure events from visit 5 until the end of follow up on December 31<sup>st</sup> 2017. We will investigate the effects of menopause on follow up attrition in the ARIC study by determining if menopausal status at the study baseline affects participant retention at Visits 4 and 5.

## References

1. Ebong IA, Watson KE, Goff DC, et al. Age at Menopause and incident heart failure: the Multi-Ethnic Study of Atherosclerosis. *Menopause*. 2014;21:585-591.
2. Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR. Association of Age at Menopause with Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis. *Journal of the American Heart Association*. 2016;5:pil: e003769.
3. Rahman I, Akesson A, Wolk A. Relationship between Age at natural menopause and risk of heart failure. *Menopause*. 2015;22:12-16.
4. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020:CIR0000000000000757-CIR0000000000000757.
5. Davis SR, Castelo-Branco C, Chedraui P, et al. Understanding weight gain at menopause. *Climacteric*. 2012;15:419-429.
6. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa new emerging team group study. *Menopause*. 2012;19:760-767.
7. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, Inflammation, and Visceral Adiposity across the Menopausal Transition: A prospective Study. *J Clin Endocrinol Metab*. 2009;94:1104-1110.
8. Ebong IA, Goff DC, Rodriguez CJ, et al. The relationship between measures of obesity and incident heart failure: The multi-ethnic study of atherosclerosis. *Obesity*. 2013;21:1915-1922.
9. Loehr LR, Rosamond WD, Poole C, et al. Association of Multiple Anthropometrics of Overweight and Obesity With Incident Heart Failure: The Atherosclerosis Risk in Communities Study. *Circ Heart Fail*. 2009;2:18-24.

10. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and Incidence of Heart Failure Hospitalization and Mortality: A Population-Based Prospective Study. *Circ Heart Failure*. 2009;2:202-208.
11. Kenchaiah S, Evans JC, Levy D, et al. Obesity And The Risk of Heart Failure. *N Engl J Med*. 2002;347:305-313.
12. Kenchaiah S, Gaziano JM, Vasan RS. Impact of obesity on the risk of heart failure and survival after the onset of heart failure. *Med Clin N Am*. 2004;88:1273-1294.
13. Voulgari C, Tentolouris N, Diaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased Heart Failure Risk in Normal-Weight People With Metabolic Syndrome Compared With Metabolically Healthy Obese Individuals. *J Am Coll Cardiol*. 2011;58:1343-1350.
14. Deswal A. Obesity, Leptin and Incident Heart Failure. *J Am Coll Cardiol*. 2011;58:1878-1880.
15. Horwich TB, Fonarow GC. Glucose, Obesity, Metabolic Syndrome, and Diabetes. *J Am Coll Cardiol*. 2010;55:283-293.
16. Ebong IA, Watson KE, Goff DC, et al. Association of menopause age and N-terminal pro brain natriuretic peptide: the Multi-Ethnic Study of Atherosclerosis. *Menopause*. 2015;22:527-533.
17. Vaduganathan M, Fonarow GC. Epidemiology of Hospitalized Heart Failure. Differences and Similarities Between Patients with Reduced versus Preserved Ejection Fraction. *Heart Fail Clin*. 2013;9:271-276.
18. Knowlton A. Estrogen and cardiovascular disease: aging and estrogen loss at the heart of the matter? *Future Cardiol*. 2012;8:9-12.

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

- 1a. Early menopause will be associated with greater risk of incident heart failure. The relationship between early menopause and incident heart failure will be significantly moderated by central obesity.
- 1b. Early menopause will be associated with greater risk of incident heart failure. The relationship between early menopause and incident heart failure will be significantly moderated by generalized obesity.
2. Early menopause will be associated with greater risk of heart failure with preserved ejection fraction than heart failure with reduced ejection fraction.

**6. Design and analysis:**

**Study design:** Cohort study

## **Data**

Inclusion criteria: Post-menopausal women of the ARIC study. Women were considered to have reached menopause if they were older than 55 years of age or had undergone a bilateral oophorectomy and/or self-reported being postmenopausal or absence of menstrual periods in the preceding year.

Exclusion criteria: Women who were missing information on menopause age, measurements of central or generalized obesity and HF status at the end of follow up. We will also exclude women with prevalent HF at ARIC exam 5 and those who had undergone hysterectomy without bilateral oophorectomy before the onset of menopause or when younger than 55 years of age due to inability to accurately estimate their menopause age.

## **Variable types:**

### **Study hypothesis 1a:**

1. Predictor variable: Early menopause (and menopause age) measured from visit 4 data.
2. Outcome variable: Incident heart failure, follow up time in years
3. Effect modifier: Central obesity will be indicated by waist circumference. Women will be classified as having central obesity if waist circumference is >88 cm

### **Study hypothesis 1b:**

1. Predictor variable: Early menopause (and menopause age) measured from visit 4 data.
2. Outcome variable: Incident heart failure, follow up time in years
3. Effect modifier: Generalized obesity will be indicated by body mass index. Women were classified as normal weight if BMI was  $\geq 18.5$  but  $< 25$  kg/m<sup>2</sup>, overweight if BMI was 25-29.9 kg/m<sup>2</sup>, obese if BMI was 30-39.9 kg/m<sup>2</sup> and severely obese if BMI was  $\geq 40$  kg/m<sup>2</sup>

### **Study hypothesis 2:**

1. Predictor variable: Early menopause (and menopause age) measured from visit 4 data.
2. Outcome variable: Incident heart failure subtype, follow up time in years

### **Covariates (from exam 5 data):**

1. Confounders (exam 5 data): age, race, educational status, cigarette smoking and center
2. Traditional CVD risk factors (exam 5 data): systolic blood pressure, antihypertensive medication use, hypertension, diabetes, total cholesterol, high density lipoprotein-cholesterol, triglyceride, sports-index physical activity.

3. History of myocardial infarction at ARIC visit 5
4. Menopause related variables:
  - a. Self-report of being postmenopausal
  - b. Age at menopause
  - c. Number of periods in last 12 months
  - d. Date of last menstrual period
  - e. Self-report of hysterectomy
  - f. Self-report of bilateral oophorectomy

**Analytical plan:**

This study will include postmenopausal women in the ARIC study with data on menopause age at visit 5 and records of incident heart failure data during follow up. Descriptive statistics will be used to present characteristics of study participants according to categories of generalized and central obesity (indicated by body mass index and waist circumference respectively) using means  $\pm$  SD, median (interquartile range) and percentages as appropriate at visit 5. Comparisons will be made between the early menopause groups using Chi-squared test, ANOVA and Kruskal Wallis test as appropriate. Variables with highly skewed distributions will be log-transformed. Kaplan-Meier plots for incident HF will be presented according to categories of early menopause separately for generalized and central obesity and tested with the Log-rank test.

For study hypothesis 1a, we will use Cox Proportional hazards techniques to model the associations of early menopause, central obesity and incident HF with other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional heart failure risk factors. We will test for the presence of interactions between early menopause and central obesity.

For study hypothesis 1b, we will use Cox Proportional hazards techniques to model the associations of early menopause, generalized obesity and incident HF with other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. We will test for the presence of interactions between early menopause and generalized obesity.

For study hypothesis 2, we will use Cox Proportional hazards techniques to model the associations of early menopause with incident heart failure subtypes and other covariates. We will adopt a sequential adjustment process incorporating confounders and traditional CVD risk factors. In testing all 3 hypotheses, we will evaluate for the proportionality of hazards assumption by visually examining the log-log plots. Two-sided p-values of  $<0.05$  will be considered significant.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript?  No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES\_OTH and/or RES\_DNA = "ARIC only" and/or "Not for Profit" ?  
Not applicable

8.a. Will the DNA data be used in this manuscript?  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES\_DNA = "No use/storage DNA"? Not applicable

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.  Yes

10. What are the most related manuscript proposals in ARIC? Association of Age at Menopause with Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis by Duke Appiah.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  No

11.b. If yes, is the proposal: Not applicable

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.

