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Age at Menopause and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To evaluate associations of early menopause (menopause occurring before 45 years of age) and age at menopause with incident heart failure (HF) in post-menopausal women. We also explored associations of early, and age at menopause with left ventricular (LV) measures of structure and function in post-menopausal women.

Methods—We included 2947 post-menopausal women, aged 45-84 years, without known cardiovascular disease (2000-2002), from the Multi-Ethnic study of Atherosclerosis. Cox-Proportional hazards models were used to examine associations of early, and age at menopause with incident HF. In 2123 post-menopausal women in whom cardiac magnetic resonance imaging was obtained at baseline, we explored associations of early, and age at menopause with LV measures using multivariable linear regression.

Results—Over a median follow-up of 8.5 years, we observed 71 HF events. There were no significant interactions with ethnicity for incident HF ($P_{\text{interaction}} > 0.05$). In adjusted analysis, early menopause was associated with increased risk of incident HF [1.66 (1.01-2.73)], while each year increase in age at menopause was associated with decreased risk of incident HF [0.96 (0.94-0.99)].

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We observed significant interactions between early menopause and ethnicity for LV mass to volume ratio (LVMVR), $P_{\text{interaction}}=0.02$. In Chinese-American women, early menopause was associated with higher LVMVR (+0.11, $p=0.0002$), while each year increase in age at menopause was associated with lower LVMVR (-0.004 , $p=0.04$) at baseline.

Conclusion—An older menopausal age is independently associated with decreased risk of incident HF. Concentric LV remodelling, indicated by a higher LVMVR was present in Chinese-American women with early menopause at baseline.

Keywords

Menopause; Heart failure; Estrogen

Introduction

Prior studies have investigated the relationship between menopause and cardiovascular disease (CVD),¹⁻³ but the results have been inconsistent and the direct causal relationship between menopause and increased cardiovascular risk is still debated.⁴ Early menopause (menopause occurring before 45 years of age) has been linked to increased cardiovascular risk⁴ and the age at menopause may be an indicator of biologic aging.² The increase in cardiovascular risk at menopause may be a consequence of estrogen deprivation,³⁻⁵ or result from a higher prevalence of cardiovascular risk factors such as hypertension,^{3, 6} diabetes,^{3, 4, 7, 8} visceral obesity,^{4, 7, 9} insulin resistance^{7, 8} dyslipidemia^{3, 4, 7, 8} and endothelial dysfunction⁴ which occur with aging.³

Amidst the ongoing studies investigating the relationship between menopause and CVD, the association between age at menopause and heart failure (HF) is yet to be investigated. There are gender-related differences in the anatomy and physiology of the myocardium¹⁰ and there could also be differences in HF in women when compared to men. HF with preserved ejection fraction (HFpEF) or diastolic dysfunction occurs more commonly in women than men.^{5, 11} Estrogen has multiple effects on the cardiovascular system^{5, 12} and its deficiency may contribute to gender differences in the pathogenesis and progression of CVD^{8, 10} including HF in the post-menopausal period.

Studies involving small sample sizes have indicated that menopause may be associated with impaired left ventricular (LV) systolic and diastolic cardiac function.¹³⁻¹⁶ However, the relationship between age at menopause and LV measures of structure and function has not been studied in large population-based cohorts. We evaluated the associations of early, and age at menopause with incident HF in post-menopausal women enrolled in the Multi-Ethnic study of atherosclerosis (MESA). We also explored the associations of early, and age at menopause with LV measures of structure and function obtained by magnetic resonance imaging (MRI) in post-menopausal women at MESA baseline.

Methods

Study Population

MESA is a population-based cohort of 6814 participants (including 3601 women) of White (38%), African-American (28%), Chinese (12%) and Hispanic (22%) descent, aged 45-84 years (2000-2002), and without clinical CVD at baseline. The aim of MESA was to study characteristics of subclinical CVD and risk factors that predict progression to clinically overt CVD or progression of the subclinical disease. Participants were enrolled from six locations in the US. MESA's design and objectives have been published.¹⁷ The protocol was approved by institutional review boards at participating centers and informed consent was obtained from participants. This substudy included 2949 post-menopausal women and utilized baseline and HF data collected and adjudicated as of October 2012. We had a sample size of 2947 after excluding 2 women who were missing information on their HF status.

Baseline Measurements

Standardized questionnaires were used to collect information on menopause, age at menopause, ethnicity, educational status, cigarette smoking, number of pregnancies, history of oophorectomy, use of hormone therapy (HT), hypertension, diabetes, and medications. Women were asked if they had gone through “menopause” or “change of life” and required to state the age at which they experienced menopause. Women who reported that they were going through menopause at baseline were asked to provide the date of their last menstrual period and the number of periods they had experienced in the last twelve months. Women who did not experience menstruation for twelve or more months before baseline were classified as being post-menopausal. Participants were classified as having early menopause if they experienced menopause before 45 years of age. Weight was measured to the nearest 0.5 kg with a balance scale. Height was measured to the nearest 0.1 cm with a stadiometer. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2) and used to indicate generalized obesity. Waist and hip circumferences were measured to the nearest 0.1 cm with a measuring tape at the umbilicus and maximum hip diameter respectively. Waist-hip ratio (WHR) was calculated by dividing waist by hip circumference and used to indicate visceral obesity.¹⁸ Three measurements of resting blood pressure (BP) were obtained using a Dinamap automated sphygmomanometer and the average of the second and third readings was used. Hypertension was defined as systolic BP ≥ 140 mm hg or diastolic BP ≥ 90 mm hg or use of antihypertensive medications.

Fasting plasma glucose and insulin were measured by the glucose-oxidase and radioimmunoassay methods respectively.^{19, 20} Diabetes was defined as fasting glucose ≥ 126 mg/dl or use of hypoglycemic medications.²⁰ Insulin resistance (indicated by homeostasis model assessment, HOMA-IR) was calculated as $\text{fasting glucose (mmol/l)} \times \text{fasting insulin (}\mu\text{U/ml)} / 22.5$.²⁰ Triglyceride and high density lipoprotein-cholesterol (HDL-C) were measured by a glycerol-blanked enzymatic method and cholesterol-oxidase reaction respectively using fasting plasma samples.¹⁹ Metabolic syndrome (MS) is the clinical surrogate of insulin resistance²¹ and was defined according to the National Cholesterol Education Program Adult Treatment Panel III as consisting of three or more of the following metabolic abnormalities: central obesity (waist circumference >102 cm in men and >88 cm

in women), high triglyceride (≥ 150 mg/dl), low HDL-C (<40 mg/dl in men and <50 mg/dl in women), high blood pressure ($\geq 130/85$ mmHg) or being on antihypertensive medications and high fasting blood glucose (≥ 100 mg/dl) or being on antidiabetic medications.²²

Interleukin-6 was the inflammatory marker with the strongest prediction for incident HF in MESA²⁰ and was measured using an ultrasensitive enzyme-linked immunosorbent assay.²³ Serum creatinine measured by colorimetry was used to estimate the creatinine-based glomerular filtration rate (eGFRcr), which is an indicator of kidney function.²⁴ Resting 12-lead electrocardiograms were obtained, centrally read and coded for the presence of LV hypertrophy (LVH) using the Minnesota coding system.

Cardiac MRI performed with 1.5-T magnets was obtained in a subset of MESA participants at baseline and available for 2123 post-menopausal women. Imaging data was read with MASS software (version 4.0, Leiden, The Netherlands). The MESA cardiac MRI protocol, image analysis, inter- and intra-reader reproducibility have been reported.²⁵ LV mass (LVM) was calculated by summation of the myocardial area multiplied by slice thickness plus image gap in the end-diastolic phase multiplied by the myocardial specific gravity. LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were determined by summing myocardial areas on each separate slice multiplied by the sum of slice thickness and image gap. LV mass to volume ratio (LVMVR) was derived by dividing LVM with LVEDV. LV stroke volume (LVSV) was derived by subtracting LVESV from LVEDV. LV ejection fraction (LVEF) was calculated by dividing LVSV with LVEDV and multiplying by 100. Details of quality control activities that were conducted at MESA field centers, coordinating centers, laboratories, ECG and MRI reading centers are available in the manual of operations at www.mesa-nhlbi.org.

Follow-up and Incident Heart Failure Definition

The median follow-up was 8.5 years (interquartile range, 0.96) with a total of 22,598 person-years of observation. Each participant or their next of kin was contacted by a telephone interviewer at 6-9 month intervals to inquire about interim hospitalizations, outpatient diagnoses and deaths due to cardiovascular causes.²⁰ Records were obtained on approximately 99% of hospitalized cardiovascular encounters and some information on 97% of outpatient diagnostic encounters. Hospital records were abstracted and reviewed by paired physicians for independent endpoint classification and assignment of incidence dates.²⁰ The reviewing pair adjudicated differences but if disagreements persisted, the morbidity and mortality classification committee made the final decision.

Our endpoint was new-onset HF. Multiple HF occurrences in the same participant were considered once and the time to the first event was used. Endpoint criteria for HF in MESA included; (1) physician-diagnosed HF and medical therapy for HF; and (2) pulmonary edema/congestion on chest radiography; or (3) dilated ventricle or poor LV function on echocardiography or ventriculography, or evidence of LV diastolic dysfunction.²⁰ Participants not meeting HF criteria, and those with a physician diagnosis only (without any other evidence) were classified as not having HF. Myocardial infarction (MI) is a potent HF risk factor²⁶ and was diagnosed based on the presence of symptoms, electrocardiographic findings and cardiac biomarker levels.²⁰

Statistical Analysis

Data are presented according to post-menopausal group using means $\pm$ standard deviations or median (interquartile range) for continuous variables and percentage for categorical variables. We calculated the incidence rates of HF per 1000 person-years of exposure in each post-menopausal group. Due to skewness, logarithmic transformation was done for triglyceride, interleukin-6, HOMA-IR and number of pregnancies. Comparisons between postmenopausal groups were tested using Chi-square (categorical variables), T-test (normally distributed continuous variables) and Mann-Whitney test (non-normally distributed continuous variables). We also compared postmenopausal women according to their incident HF status. Kaplan-Meier plots for incident HF are presented according to post-menopausal group and tested with the Log-rank test. Participants were censored if they were lost to follow-up or failed to experience incident HF at the end of follow-up.

We assessed the hazard ratios of incident HF for early, and each year increase in age at menopause using Cox-Proportional hazards models. We checked for interactions of early, and age at menopause with ethnicity for incident HF at the 0.05 significance level. We constructed unadjusted models (model 1), and age-adjusted models (model 2). In model 3, we introduced ethnicity, center, reproductive characteristics (number of pregnancies and use of HT) and known HF risk factors^{20, 26-29} including socioeconomic status (indicated by educational status), smoking, hypertension, diabetes, kidney function, obesity (indicated by BMI), LVH (by electrocardiogram), insulin resistance, inflammation and interim MI. Because we included its individual components, MS was excluded. Due to our modest number of HF events, we selected the most parsimonious model using backward elimination in which age was retained and variables were eliminated if their p was >0.10 . The resulting model included early menopause (or age at menopause), age, smoking, BMI, diabetes, hypertension, LVH, and interim MI. Participants with missing data on a variable needed for a particular model were excluded from analyses. We checked for proportionality of hazards by visually examining the log-log plots.

In exploration, we conducted cross-sectional analysis in post-menopausal women who had cardiac MRI at baseline. Because LV measures in MESA have been found to differ by ethnicity,³⁰ we calculated age-adjusted means of LV measures according to ethnicity, post-menopausal group and HT use with ANCOVA. LV measures were also adjusted for height and weight to account for the confounding effects of body size.¹⁸ LVEF and LVMVR were only age-adjusted. We calculated adjusted differences in LV measures attributable to early, and each year increase in age at menopause using multivariable linear regression. We tested for the presence of interactions of early, and age at menopause with ethnicity for all LV measures at the 0.05 significance level. We present ethnicity-stratified analyses because we observed significant interactions between early menopause and ethnicity for LVMVR ($P_{\text{interaction}}=0.02$). We adjusted for known potential confounders, height, weight, reproductive characteristics and HF risk factors. Height and weight were excluded from models for LVEF and LVMVR. BMI was excluded from models that included height and weight to avoid collinearity. We checked for linearity by visually examining the scatterplots of the R-Student residuals versus predicted values.

We performed a sensitivity analysis in the MRI cohort in which we assessed the hazard ratios of incident HF for early, and each year increase in age at menopause in models that replaced LVH determined by electrocardiogram with its corresponding MRI equivalent. In a subpopulation of 822 men and women without LVH risk factors in MESA, the 95th percentile cutoff of observed/predicted LVM of 1.31 has been accepted as corresponding to LVH.³¹ 2-sided p-values of <0.05 were considered significant. Statistical analysis was performed using SAS enterprise guide version 4.3. (SAS Institute Inc, Cary, NC).

Results

There were 195 cases (118 in men and 77 in women) of incident HF in MESA. We observed 71 events in our sample of postmenopausal women and 25 occurred in women with early menopause. The overall HF incidence amongst postmenopausal MESA women was 3.14/1000 person-years with incidences of 4.57/1000 and 2.69/1000 person-years in women with and without early menopause respectively. The HF incidence was 2.93/1000, 2.23/1000, 4.02/1000, and 2.92/1000 person-years in White, Chinese-American, African-American and Hispanic postmenopausal women respectively (supplementa table 1). Early menopause was reported by 730 participants. Women who experienced early menopause were more commonly African-American, current smokers and attained lower educational levels at baseline. Interleukin-6, BMI and HOMA-IR levels were higher, and diabetes was more prevalent in women with early menopause (table 1). Twenty-one women experienced MI prior to their HF diagnosis. There were no statistically significant differences in the occurrence of interim MI across post-menopausal groups. Postmenopausal women who developed incident HF had lower GFR, but higher BMI, WHR, HOMA-IR and interleukin-6 levels. Hypertension, diabetes and LVH were more prevalent among participants who developed incident HF. All participants who experienced MI during follow-up subsequently developed incident HF (supplemental table 2). The probability of being free from HF was significantly less in women with early menopause (figure 1). There were no significant interactions with ethnicity for incident HF ($p_{\text{interaction}} > 0.05$). In adjusted analysis, early menopause was associated with increased risk of incident HF, while each year increase in age at menopause was associated with decreased risk of incident HF (table 2).

For our exploratory analysis of the MRI cohort, we had 2123 post-menopausal women, 509 of whom had experienced early menopause. The MRI cohort included 840 Caucasian, 272 Chinese-American, 558 African-American, and 453 Hispanic women. Adjusted means of LVMVR was higher while LVEDV was lower in Chinese-American women with early menopause who were not using HT at baseline (supplemental table 3). In adjusted analysis, early menopause was associated with higher LVMVR and lower LVSV and LVEDV, while each year increase in age at menopause was associated with lower LVMVR and higher LVSV and LVEDV in Chinese-Americans (Table 3). There was no significant collinearity because the variance inflation factors and condition indices were <5 for all terms in each of the models. In sensitivity analyses of the MRI cohort in which LVH determined by ECG was replaced with its MRI equivalent, the hazard ratios of incident HF were 1.46 (0.71-2.98) and 0.97 (0.93-1.01) for early, and each year increase in age at menopause respectively after adjusting for age, smoking, BMI, diabetes, hypertension, LVH and interim MI. However, we observed only 39 events in the MRI cohort and had inadequate power to make definite

conclusions related to incident HF. Post-menopausal women who had cardiac MRI at baseline were younger, more educated, and had lower BMI and WHR than those who did not (supplemental table 4). Diabetes and hypertension were more prevalent among women who did not have cardiac MRI at baseline. The percentage of missing data was <3% for all variables, therefore, sample sizes may have varied slightly between the models.

Discussion

In this multi-ethnic population of post-menopausal women, we have shown that an older menopausal age is associated with decreased risk of incident HF. This association remained significant after adjusting for chronological age, and known HF risk factors. This finding suggests that menopause may have independent effects on the heart and a later age at menopause could delay the onset of this deleterious effect. Estrogen deficiency is pathognomonic of the post-menopausal period.^{7, 9} Consequently, the relationships of early and age at menopause with incident HF could be explained by changes in duration of exposure to endogenous estrogen.

Menopause is associated with metabolic derangements^{3, 8, 9} such as lipid abnormalities, visceral obesity, and insulin resistance which are known HF risk factors.^{27, 29, 32, 33} Women who experienced early menopause in our study had worse metabolic profiles with increased prevalence of diabetes, generalized obesity, insulin resistance and higher inflammatory markers. The reason behind these metabolic changes remains controversial because menopause is a normal consequence of aging,⁷ which is associated with an increased prevalence of cardiometabolic risk factors.³

The higher LVMVR (which indicates LV concentric remodelling)¹⁸ and lower LVSV (which is a determinant of cardiac output) observed in Chinese-American women with early menopause at baseline may be due to their lower LVEDV measures. However, in Caucasian, African-American and Hispanic women we did not observe differences in LV measures attributable to early, or each year increase in age at menopause at baseline. Our findings for Chinese-American women agrees with Kaur et al.'s study¹⁴ in which subclinical cardiac dysfunction was reported in women with earlier onset of menopause, but differs for White, African-American and Hispanic women. These similarity and differences may be related to different ethnicities of the populations being studied, but, the ethnicity of participants in Kaur et al.'s study was not specified. Moreover, the study of Kaur et al. included 50 participants and LV measures were obtained by echocardiography. We used LV measures obtained by MRI which is more accurate.¹⁸

We did not observe ethnic differences in the relationships between early, and age at menopause with incident HF. Thus, we concluded that the association with incident HF was consistent across ethnic groups. Because Chinese-American women with early menopause exhibited evidence of concentric remodelling at baseline, we speculated that they possibly manifested subclinical cardiac effects of estrogen deficiency due to menopause sooner than other ethnicities. However, this hypothesis must be explored in future studies. Despite ethnic differences observed in the association with LVMVR at baseline, the consistency in the association between age at menopause and incident HF across all ethnicities after a median

follow-up of 8.5 years could imply that the effects of menopause (and possibly estrogen deficiency) are progressive over time.

The cardiac effects of estrogen are both direct and indirect, and are mediated by estrogen receptor- α and estrogen receptor- β .^{4, 34} The direct effects include rapid vasodilatation through increased nitric oxide production,^{5, 12, 34, 35} and longer-term effects involving genomic-mediated changes in expression of proteins that regulate vascular tone and response to injury.^{12, 34} Estrogen-mediated genomic effects increase vasodilatory enzymes and accelerate endothelial cell growth,³⁴ but inhibit smooth-muscle proliferation, collagen and elastin deposition.^{10, 34} Indirect effects include actions on ventricular contractile function, endothelial calcium metabolism and coronary calcification, coagulation and fibrinolysis, insulin resistance, inflammation, oxidative alterations of lipids and changes in lipid profile.^{4, 10, 34} Estrogen increases serum levels of high density lipoprotein-cholesterol and triglycerides, and decreases low density lipoprotein-cholesterol (LDL-C) and LDL-C oxidation.³⁴ Estrogen also modulates cardiac myocyte sensitivity to autonomic stimuli and results in enhanced inotropy, decreased chronotropy and reduced cardiac respiratory and energy needs.¹⁰ These effects support a myocardial protective role for estrogens which is lost after the onset of menopause.

To the best of our knowledge, our study is the first to demonstrate associations of early, and age at menopause with incident HF. Other strengths of our study include its prospective nature, the availability of a multi-ethnic sample without clinical CVD at baseline and highly standardized data collection methods. Our study has limitations. Estrogen levels were not measured at baseline. The postmenopausal period is also associated with changes in ovarian androgen production and a state of relative androgen predominance.⁹ Circulating androgen levels were not measured at baseline. Age at menopause was based on self-report and variations in the onset and abruptness of menopause³⁶ could lead to recall bias. However, reliability and validity studies have shown that women can recall their age at menopause with accuracy.³⁷ Due to modest number of events, we had inadequate power for analysis according to HF subtypes (HFpEF or reduced EF) or type of menopause (natural or artificial). Surgical menopause due to oophorectomy was reported by 783 women. However, we had no information on artificial menopause due to chemotherapy, radiotherapy, autoimmune illness or pelvic infections. Electrocardiography has limited sensitivity for diagnosing LVH.³¹ Due to sample-size limitations, we used the full sample and electrocardiographic measurements of LVH for our primary analysis. We adjusted for interim MI, but the absence of MI does not exclude subclinical myocardial ischemia. Only few women with early menopause were taking HT at baseline, thus we had limited power to present our fully adjusted models for LV measures in the MRI cohort according to HT use. We had inadequate power for our sensitivity analysis related to incident HF in the MRI cohort, thus caution must be applied to interpretations related to this sensitivity analysis.

Conclusion

An older menopausal age is associated with decreased risks of incident HF. Concentric LV remodelling indicated by a higher LVMVR was present in Chinese-American women with early menopause at baseline. It is debatable whether the cardiac changes that result in HF in

the post-menopausal period are primarily due to ageing or result from estrogen deficiency. However, menopausal age may be an indicator of increased HF risk and signal a need for more frequent screening and aggressive risk factor modification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Heart Failure free probability in MESA women according to post-menopausal group

Figure 1.

Early menopause refers to menopause occurring before 45 years of age. There were 730 and 2217 women with and without early menopause respectively.

Table 1

Characteristics of MESA women who were post-menopausal at baseline

Characteristics	Post-Menopausal group		<i>p</i> -value
	Early menopause present n=730	Early menopause absent n=2217	
Age, years	64.5 ± 10.0	64.7 ± 8.9	0.47
Ethnicity			<0.0001
- Whites, %	32.6	39.8	
- Chinese-Americans, %	6.3	13.4	
- African-Americans, %	37.3	25.6	
- Hispanics, %	23.8	21.2	
> High school education, %	53.4	57.9	0.04
Cigarette smoking			0.0006
- Never, %	55.0	60.1	
- Former, %	30.0	30.0	
- Current, %	15.0	10.0	
Number of pregnancies, median (IQR)	3 (3)	3(3)	0.10
Left ventricular hypertrophy by ECG, %	0.41	0.82	0.27
Hormone therapy (current user), %	34.1	31.5	0.20
Hypertension, %	53.7	50.6	0.14
Diabetes, %	14.8	11.7	0.03
Triglycerides, median (IQR), mg/dl	115.0 (78.0)	113.5 (81.5)	0.21
High density lipoprotein cholesterol, mg/dl	56.1 ± 15.2	56.8 ± 15.4	0.28
Interleukin-6, ^a pg/ml	1.41 ± 1.94	1.29 ± 1.92	0.002
eGFRcr, ml/min/1.73 m ²	76.5 ± 16.9	75.3 ± 15.7	0.07
Body mass index, kg/m ²	29.42 ± 6.34	28.37 ± 5.91	<0.001
Waist-hip ratio	0.912 ± 0.08	0.907 ± 0.08	0.13
HOMA-IR ^a	2.06 ± 1.92	1.94 ± 1.87	0.03
Metabolic Syndrome, %	40.2	45.5	0.01
Incident Heart Failure, %	3.4	2.1	0.04
Interim myocardial infarction, %	2.3	1.5	0.13

Early menopause was present if menopause occurred before 45 years.

Values are expressed as means ± standard deviation unless otherwise indicated; missing values were less than 3% for all variables; *p*-values were determined using chi-squared test (categorical variables), 2-sample T-test (normally distributed continuous variables) and Mann-Whitney test (non-normally distributed continuous variables).

Abbreviations: ECG, electrocardiogram; eGFRcr, creatinine-based estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment for insulin resistance; IQR, interquartile range.

^aValues are geometric mean of interleukin-6 and HOMA-IR.

Table 2

Associations of early, and each year increase in age at menopause with incident heart failure in post-menopausal MESA women

	Early Menopause	<i>p</i>-value	Age at Menopause	<i>p</i>-value
	HR (95% CI)		HR (95% CI)	
Model 1	1.70 (1.05-2.77)	0.03	0.96 (0.93-0.99)	0.02
Model 2	1.68 (1.03-2.73)	0.04	0.96 (0.93-0.99)	0.02
Model 3	1.66 (1.01-2.73)	0.04	0.96 (0.94-0.99)	0.04

Early menopause was present if menopause occurred before 45 years. There were 2947 post-menopausal women at baseline and 730 experienced menopause before 45 years of age.

Model 1: Unadjusted analysis

Model 2: Model 1, adjusted for age

Model 3: Model 2, adjusted for smoking, body mass index, diabetes, hypertension, left ventricular hypertrophy by electrocardiogram, and interim myocardial infarction

Hazard ratios are estimated using Cox-Proportional hazards models. Variable selection was done using backward elimination in which variables were eliminated if their $p > 0.10$.

Table 3

Adjusted differences in left ventricular measures associated with early, and each year increase in age at menopause after multivariable linear regression in post-menopausal MESA women at baseline

LV measure	Early menopause	P-value	Age at menopause	P-value
End-diastolic mass (g)				
- Whites	0.40 (−3.20 – 3.99)	0.83	0.008 (−0.24 – 0.26)	0.95
- Chinese-Americans	2.17 (−2.97 – 7.32)	0.41	0.03 (−0.32 – 0.39)	0.85
- African-Americans	−0.34 (−4.96 – 4.27)	0.88	0.11 (−0.19 – 0.42)	0.47
- Hispanics	−1.81 (−6.56 – 2.94)	0.45	0.19 (−0.14 – 0.51)	0.26
End-diastolic volume (ml)				
- Whites	0.95 (−2.58 – 4.49)	0.60	−0.01 (−0.26 – 0.23)	0.92
- Chinese-Americans	−6.75 (−11.90 – [−1.59])	0.01	0.36 (0.01 – 0.72)	0.04
- African-Americans	0.87 (−3.42 – 5.16)	0.69	0.15 (−0.13 – 0.43)	0.29
- Hispanics	−1.94 (−5.82 – 1.93)	0.33	0.13 (−0.13 – 0.40)	0.33
Mass to volume ratio^a (g/ml)				
- Whites	0.004 (−0.03 – 0.04)	0.84	−0.0007 (−0.003 – 0.002)	0.53
- Chinese-Americans	0.11 (0.05 – 0.16)	0.0002	−0.004 (−0.008 – [−0.0002])	0.04
- African-Americans	−0.01 (−0.06 – 0.03)	0.52	−0.0005 (−0.003 – 0.002)	0.72
- Hispanics	0.004 (−0.04 – 0.05)	0.88	0.00006 (−0.003 – 0.003)	0.97
End-systolic volume (ml)				
- Whites	0.70 (−1.36 – 2.75)	0.51	−0.02 (−0.16 – 0.13)	0.81
- Chinese-Americans	−1.54 (−4.22 – 1.13)	0.26	0.07 (−0.11 – 0.26)	0.44
- African-Americans	0.10 (−2.35 – 2.55)	0.94	0.06 (−0.11 – 0.22)	0.49
- Hispanics	−0.54 (−2.82 – 1.73)	0.64	0.08 (−0.08 – 0.23)	0.32
Ejection fraction^a (%)				
- Whites	−0.19 (−1.47 – 1.08)	0.76	0.009 (−0.08 – 0.10)	0.84
- Chinese-Americans	−0.39 (−2.43 – 1.65)	0.71	0.05 (−0.09 – 0.19)	0.52
- African-Americans	0.23 (−1.17 – 1.63)	0.75	−0.02 (−0.11 – 0.07)	0.67
- Hispanics	0.30 (−1.08 – 1.68)	0.67	−0.04 (−0.14 – 0.05)	0.36
Stroke volume (ml)				
- Whites	0.26 (−2.29 – 2.81)	0.84	0.005 (−0.17 – 0.18)	0.96
- Chinese-Americans	−5.20 (−9.26 – [−1.15])	0.01	0.29 (0.01 – 0.57)	0.04
- African-Americans	0.77 (−2.28 – 3.82)	0.62	0.09 (−0.11 – 0.29)	0.36
- Hispanics	−1.40 (−4.20 – 1.40)	0.33	0.05 (−0.14 – 0.24)	0.58

Early menopause was present if menopause occurred before 45 years. 2123 post-menopausal women obtained cardiac MRI at baseline and 509 of them had experienced menopause before 45 years of age.

Estimates are differences (β -coefficients) associated with a 1 year increase in age at menopause, and between the early menopausal and non-early menopausal group.

Estimates are adjusted for age, height, weight, educational status, cigarette smoking, center, number of pregnancies, use of hormone therapy, diabetes, high density lipoprotein-cholesterol, triglyceride, waist-hip ratio, homeostasis model assessment for insulin resistance, interleukin-6, creatinine-based estimate of glomerular filtration rate, systolic blood pressure, diastolic blood pressure and antihypertensive medication use.

^a Body mass index was included but height and weight were excluded in models for mass to volume ratio and ejection fraction.