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The Association of Menopausal Age and NT-proBrain Natriuretic Peptide: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Menopausal age could affect the risk of developing cardiovascular disease (CVD). The purpose of this study was to investigate the associations of early menopause (menopause occurring before 45 years of age) and menopausal age with NT-pro brain natriuretic peptide (NT-proBNP), a potential risk marker of CVD and heart failure (HF).

Methods—Our cross-sectional study included 2275 postmenopausal women, aged 45–85 years, without clinical CVD (2000–2002), from the Multi-Ethnic Study of Atherosclerosis. Participants were classified as having or not having early menopause. NT-proBNP was log-transformed. Multivariable linear regression was used for analysis.

Results—There were 561 women with early menopause. The median NT-proBNP value was 79.0 (41.1–151.6) pg/ml for all participants with values of 83.4 (41.4–164.9) pg/ml and 78.0 (40.8–148.3) pg/ml for women with and without early menopause respectively. The mean (SD) age was 65 (10.1) and 65 (8.9) years for women with and without early menopause respectively. There were no significant interactions between menopausal age and ethnicity. In multivariable analysis, early menopause was associated with a 10.7% increase in NT-proBNP while each year increase in menopausal age was associated with a 0.7% decrease in NT-proBNP.

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Conflicts of interest. None

Conclusion—Early menopause is associated with greater NT-proBNP levels while each year increase in menopausal age is associated with lower NT-proBNP levels in postmenopausal women.

Keywords

Menopause; NT-proBNP; Sex hormones

Introduction

Early menopause has been linked with greater cardiovascular disease (CVD) risk,^{1–3} and shown to be associated with a greater incidence of heart failure (HF),⁴ coronary artery disease and stroke.⁵ CVD is the leading cause of death in women⁶ and early diagnosis is useful for optimization of care and improvement in therapy.⁷ There are currently no biomarkers for identifying women with early menopause who are more prone to developing CVD. Sex hormones could affect natriuretic peptide levels⁸ and the postmenopausal period is defined by hormonal changes such as estrogen deficiency and relative androgen predominance.⁹ NT-pro brain natriuretic peptide (NT-proBNP) is a biomarker for the diagnosis, prognosis and management of patients with CVD and HF.^{7, 10–12} NT-proBNP can easily be measured in the clinical setting and may be a useful marker of high risk women with early menopause.

Some factors that affect NT-proBNP such as age,¹³ smoking,¹⁴ ethnicity¹⁵ and body mass index (BMI)^{8, 11, 13, 16, 17} could also affect menopausal age.^{18–21} Women have greater NT-proBNP than men^{8, 13} and menopause, a consequence of aging²² occurs specifically in women. It is not known if a woman's menopausal age is associated with NT-proBNP after accounting for traditional CVD risk factors. Examination of the relationships between menopausal age and NT-proBNP could also provide insight into the mechanisms underlying increased CVD risk in early menopausal women. We tested the hypothesis that early menopause will be independently associated with greater NT-proBNP while each year increase in menopausal age will be independently associated with lower NT-proBNP in the multi-ethnic study of atherosclerosis (MESA). Because NT-proBNP levels are lower in African-Americans than Whites,^{15, 16} we also hypothesized that the associations of early menopause and menopausal age with NT-proBNP will vary according to ethnicity.

Methods

Study Population

MESA is a population-based cohort consisting of 6814 participants (3601 women) of White (38%), African-American (28%), Chinese-American (12%) and Hispanic (22%) descent, aged 45–84 years (2000–2002) and without clinical CVD before recruitment. MESA's design and objectives have been published.²³ The aim of MESA was to study the characteristics of subclinical CVD and risk factors that predict the progression to clinical disease. The study protocol was approved by institutional review boards at participating sites and informed consent was obtained from participants. There were 2949 postmenopausal women at baseline. We excluded 34 women who concurrently reported being

perimenopausal and 640 who did not have serum samples for NT-proBNP measurements to obtain a sample size of 2275 for our cross-sectional study. The prevalence of early menopause was similar among participants (24.7%) and women excluded (25.1%) from this study.

Baseline Measurements

Standardized questionnaires were used to collect information on menopause, ethnicity, educational status, cigarette smoking, hormone therapy (HT) use, medications, hypertension, diabetes, and prior oophorectomy. Women were asked if they had experienced “menopause” or “change of life” and inquired as to the age at which they experienced menopause. Women who reported that they were perimenopausal were asked to provide the date of their last menstrual period and the number of periods they had experienced in the last twelve months. Menopause was defined as the absence of periods for at least twelve months in the absence of pregnancy. Participants were classified as having early menopause if they experienced menopause before 45 years of age.

BMI was calculated as weight divided by the square of height (kg/m^2). Hypertension was defined as systolic blood pressure (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.^{24, 25} Diabetes was defined as fasting plasma glucose ≥ 126 mg/dl or use of hypoglycemic medications.²⁵ Insulin resistance, indicated by homeostasis model assessment (HOMA-IR) was calculated as fasting glucose (mmol/l) $\times$ fasting insulin ($\mu\text{U/ml}$)/22.5.²⁵ High density lipoprotein-cholesterol (HDL-C) was measured by a cholesterol-oxidase reaction using fasting samples.²⁴ Interleukin-6 was measured with an ultrasensitive enzyme-linked immunosorbent assay.²⁶ Serum creatinine measured by colorimetry was used to estimate the creatinine-based glomerular filtration rate (eGFRcr).²⁷ Resting 12-lead electrocardiograms (ECG) were obtained, centrally read and coded for the presence of left ventricular hypertrophy (LVH) using the Minnesota coding system.²⁸ Left ventricular mass (LVM) measured by magnetic resonance imaging (MRI) was available in a subset of participants. The MESA cardiac MRI protocol, image analysis, inter- and intrareader reproducibility have been reported.²⁹

NT-proBNP was measured using an Elecsys electrochemiluminescence immunoassay based on a double-antibody sandwich method (Roche Diagnostics Corporation, Indianapolis, IN) with an intra- and interassay coefficient of variation of 2.7% and 3.2% at 175 pg/ml, 2.4% and 2.9% at 355 pg/ml, 1.9% and 2.6% at 1068 pg/ml, and 1.8% and 2.3% at 4962 pg/ml respectively.¹⁵ Analyses were performed at the core-lab (University of California, San Diego) using a 250 μl serum sample that was previously unfrozen or thawed only once.¹⁵ Details of quality control procedures conducted at MESA coordinating center, field centers, laboratories and reading centers are available in the manual of operations at www.mesa-nhlbi.org.

Statistical Analysis

Due to skewing, we performed natural logarithmic transformations for NT-proBNP. We grouped participants according to their early menopausal status and made comparisons

between them using Chi-square or Students T-test as appropriate. We also stratified participants by the median of NT-proBNP and made comparisons across the strata. Box-plots were used to present distributions of NT-proBNP according to ethnicity in both postmenopausal groups. We tested for differences in the median of NT-proBNP among ethnicities in each group using the Kruskal-Wallis test. Mann-Whitney tests were used to directly compare one ethnic group against another. In women of similar age and menopausal status, we compared NT-proBNP levels in those with and without current smoking and diabetes.

Using multivariable linear regression, we calculated differences in log NT-proBNP associated with early menopause and each year increase in menopausal age. We tested for interactions of early menopause and menopausal age with ethnicity. We present ethnic-pooled analyses because the interaction terms of early menopause, and menopausal age with ethnicity were not statistically significant ($P_{\text{interaction}}$ of 0.47 and 0.56 respectively). We adopted a sequential adjustment process. In model 1, we adjusted for age and BMI. In model 2, we included ethnicity. In model 3, we incorporated potential confounders known to affect NT-proBNP from previous literature including; smoking,^{8, 14, 17} diabetes,^{8, 17} HDL-C,¹⁷ GFR,^{8, 17} systolic BP,^{8, 17} diastolic BP^{8, 17} and antihypertensive medication use^{8, 17} and covariates that were associated with NT-proBNP at $P < 0.10$ in univariate analysis like educational status and interleukin-6. In model 4, we also included LVH.^{17, 30, 31}

Because ECG has limited sensitivity for diagnosing LVH,³² we conducted sensitivity analysis in MRI participants in which we replaced LVH by ECG with its MRI equivalent (model 5). Women who had MRI were younger and had lower BMI.⁴ In a subpopulation of MESA participants without LVH risk factors, the 95th percentile cutoff of observed/predicted LVM of 1.31 has been accepted as corresponding to LVH.³² BMI is an indicator of generalized obesity but does not distinguish between muscle or fat mass.³³ Therefore, we also constructed models in which BMI was replaced with WC, a stronger predictor of CVD³⁴ and measure of central obesity.³⁵ Hyperinsulinemia has been associated with lower natriuretic peptide levels,⁸ so we accounted for insulin resistance in non-diabetic participants by including HOMA-IR in our models.

We expected older women to have worse recollection of their menopausal age so we performed analysis that excluded women who were older than 65 years of age. We checked for linearity by visually examining scatter plots of R-student residuals versus predicted values. Participants missing data on a variable needed for a particular model were excluded from analyses. 2-sided p-values of < 0.05 were considered significant. Statistical analyses were performed using SAS enterprise guide version 5.1 (SAS institute Inc, Cary, NC).

Results

Out of 2275 postmenopausal women, 561 experienced early menopause. The median NT-proBNP value was 79.0 (41.1–151.6) pg/ml for all participants with values of 83.4 (41.4–164.9) pg/ml and 78.0 (40.8–148.3) pg/ml for women with and without early menopause respectively. Women with early menopause were more likely to have diabetes and greater BMI and interleukin-6 levels. Smoking was more prevalent in the early menopausal group

(table 1). Women with greater NT-proBNP were older, more commonly White and likely to have hypertension. BMI was lower while interleukin-6 was greater in women with greater NT-proBNP. There were no differences in the use of HT across strata of NT-proBNP (supplemental table 1). In women of similar age and menopausal status, the differences in NT-proBNP between smokers and non-smokers were mostly not significant. Although the difference was not always significant, NT-proBNP generally appeared lower in those with diabetes than those without amongst women of similar age and menopausal status (supplemental table 2).

The prevalence of early menopause was 20.9%, 13.3%, 33.6% and 27.8% for White, Chinese-American, African-American and Hispanic women respectively. We observed differences in the medians of NT-proBNP among ethnicities in women with and without early menopause with p -values of 0.0002 and <0.0001 respectively (figures 1a and 1b). In women with early menopause, the medians of NT-proBNP were significantly greater in Whites when compared to African-Americans ($p < 0.0001$) and Hispanics ($p = 0.007$). In those without early menopause, the medians of NT-proBNP were significantly greater in Whites when compared to Chinese-Americans ($p < 0.0001$), African-Americans ($p < 0.0001$) and Hispanics ($p < 0.0001$). The medians of NT-proBNP were also significantly greater in Hispanics when compared to Chinese-Americans ($p = 0.03$) and African-Americans ($p < 0.0001$) in women without early menopause. Current cigarette smoking and hypertension were most common in African-Americans in both postmenopausal groups. BMI was greatest in African-Americans but lowest in Chinese-Americans in both postmenopausal groups (supplemental tables 3 and 4).

Early menopause was associated with a 10.7% increase in NT-proBNP while each year increase in menopausal age was associated with a 0.7% decrease in NT-proBNP (model 4, table 2). Similar estimates were obtained when LVH was replaced by LVM (model 5, table 2). Our point estimates were similar when BMI was substituted with WC because early menopause was associated with a 10.7% increase in NT-proBNP while each year increase in menopausal age was associated with a 0.8% decrease in NT-proBNP. In women without diabetes ($n = 1987$) the estimates did not differ much because early menopause was associated with a 7.3% increase in NT-proBNP while each year increase in menopausal age was associated with a 0.7% decrease in log NT-proBNP. In analysis involving women aged 65 years and younger, the patterns of association remained similar (table 3).

We presented ethnic-specific analysis in supplemental table 5. Due to inadequate power, we cannot make definite conclusions but the percentage differences in NT-proBNP associated with early menopause tended to be greater in African-Americans. We advise caution in interpretations related to this analysis particularly in Chinese-Americans and recommend that ethnic-specific analysis should be pursued in adequately powered studies. There was no significant collinearity because the variance inflation factors and the condition indices were < 5 for all terms in each of our models. The percentage of missing values was $< 3\%$ for all variables, therefore, sample sizes may have varied slightly between the models.

Discussion

In our multi-ethnic sample of postmenopausal women without clinical CVD, early menopause was associated with greater NT-proBNP while each year increase in menopausal age was associated with lower NT-proBNP. This association was significant after adjusting for CVD risk factors and consistent in non-diabetic and younger participants. Our findings remained consistent when LVH was assessed by MRI which is a more sensitive measure of cardiac remodelling.³² Our findings agree with our prior study which showed that early menopause is associated with an increased risk of incident HF.⁴ NT-proBNP has been linked to an increased risk of future HF¹⁵ and reliably predicts HF in multiple ethnicities.¹⁵

Early menopause was most common in African-Americans and least common in Chinese-Americans. We observed ethnic variations in NT-proBNP because greater levels were observed in White women relative to other ethnicities. However, we failed to observe significant interactions with ethnicity suggesting that the association of menopausal age and NT-proBNP may be consistent across ethnic groups. Because the associations appeared stronger when we accounted for ethnicity, we concluded that ethnicity negatively confounds the association between menopausal age and NT-proBNP.

Menopause is associated with an increase in fat mass^{36, 37} and early menopausal women in our study accordingly had greater BMI values. Obesity (particularly BMI) is inversely associated with NT-proBNP.¹⁷ Despite the fact that our study findings supported our hypothesis, It would also seem reasonable to speculate that early menopause which was characterized by greater BMI could be associated with lower NT-proBNP. However, early menopause was significantly associated with greater NT-proBNP in models that included BMI so we considered that BMI was a confounder of this association which was possibly mediated by another unmeasured factor.

Hormonal changes likely contribute to changes in natriuretic peptide levels after menopause.⁸ Menopause is characterized by estrogen deficiency^{9, 22} and women with early menopause would have a shorter duration of exposure to endogenous estrogens. Estrogen loss has multiple effects on the heart³⁸⁻⁴⁰ and vasculature;^{39, 40} one of which involves activation of the renin-angiotensin-aldosterone system (RAAS).^{8, 38} Chronic activation of RAAS increases oxidative stress and reduces nitric oxide bioavailability in estrogen sensitive tissues resulting in endothelial dysfunction, inflammation and immune dysfunction.³⁸ These processes impair myocardial relaxation and LV compliance³⁸ and are known pathways for the development of HF⁴¹ and CVD.^{2, 22, 42}

Natriuretic peptides are produced from cardiac myocytes as a result of increased wall distension, stretching and neurohormonal activation^{7, 10} that results from reduced ventricular compliance. Natriuretic peptides have proangiogenic, antihypertrophic and vasodilatory effects on the cardiovascular system and are also counter-regulators of RAAS and the adrenergic systems.^{7, 8, 13, 16} Increased NT-proBNP may indicate cardioprotective actions^{8, 13, 16} against the deleterious effects of estrogen loss on the hearts of early menopausal women. Other sex hormones such as testosterone and progesterones could also

contribute to cardioprotective mechanisms⁴³ in the hearts of postmenopausal females. Sex hormones were not measured in this study and should be explored in future studies.

The onset of menopause is associated with greater prevalence of metabolic abnormalities^{22, 42, 44} and CVD risk factors.^{45, 46} Women with early menopause in our study were more likely to have diabetes, greater BMI and indices of inflammation. Accordingly, we considered that elevated NT-proBNP could indicate subclinical cardiac remodelling¹⁰ resulting from a hypoestrogenic state⁴⁰ and worse CVD profile in women with early menopause. Lipid abnormalities in the postmenopausal period^{2, 22, 45} causes increased circulating free fatty acids and altered fatty acid metabolism in cardiomyocytes could induce cardiac lipotoxicity.^{22, 41} Lipotoxicity results in apoptosis of cardiomyocytes and cardiac dysfunction⁴¹ which stimulates natriuretic peptide release by inducing elevated filling pressures in the heart.¹⁰

In comparisons across similar age and postmenopausal groups, our findings appeared different from studies that reported elevated NT-proBNP in smokers.¹⁴ The tendency towards lower NT-proBNP in diabetic women agrees with reports of inverse associations between plasma glucose and NT-proBNP.^{30, 47} But, elevated NT-proBNP has also been reported in diabetic individuals with HF⁴⁸ and vascular complications.⁴⁹ Diabetes^{50–53} and smoking^{14, 54} cause cardiac changes through multiple mechanisms including inflammation. Chronic inflammation promotes myocardial fibrosis and adverse remodelling⁵³ which are precursors of LVH.⁵⁵ LVH is associated with elevated NT-proBNP^{30, 31} and a precursor to HF.⁵⁵ Collectively, we surmised that ultimately risk factors would adversely affect remodelling which is associated with NT-proBNP elevation.

This is the first study to demonstrate associations between menopausal age and NT-proBNP. Other strengths include the availability of a multi-ethnic population without clinical CVD and highly standardized data collection methods. We acknowledge limitations. The cross-sectional nature of our analyses limits our ability to establish causality or temporality. There is a possibility of residual confounding from unmeasured sex hormones and risk factors. Measurement error could arise because menopausal status was determined by self-report particularly in older participants. But, women have recalled their menopausal age with accuracy⁵⁶ and our associations appeared consistent in younger participants. Due to a limited number of participants in ethnic subgroups and inadequate power, we were unable to draw inferences from our ethnic-specific analysis. Although 783 women provided information on artificial menopause resulting from oophorectomy, we had no information on chemotherapy, radiotherapy, autoimmune illness or pelvic infections and did not perform subgroup analyses according to type of menopause (natural or artificial).

Amongst early menopausal women, 268 experienced menopause before 40 years of age and were characterized as having premature menopause. We had inadequate power for subgroup analyses according to the severity of early menopause. Genetics could affect a woman's age at menopause²¹ and response to myocardial stress.¹⁵ We did not explore the effects of genetic factors but the role of genetics on CVD development in early menopausal women should be explored in future studies. NT-proBNP has marked intra-individual variability¹² which could affect the reliability of its measurement. MESA women were aged 45 years and

above at baseline therefore those who were yet to experience menopause were younger and would subsequently belong to the non-early menopausal group. This could generate sampling bias and caution must be maintained when generalizing our findings to younger populations.

Conclusion

In our multi-ethnic sample of postmenopausal women without clinical CVD, early menopause is associated with greater NT-proBNP while each year increase in menopausal age is associated with lower NT-proBNP. NT-proBNP may be a useful screening test to detect high risk women with early menopause. Even modest NT-proBNP elevations offer prognostic value before the development of clinical CVD.⁵⁷ Longitudinal studies are needed to detect mechanisms of disease and to see how early menopause affects NT-proBNP over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Data points represent median (25th and 75th percentile) for each ethnicity. Differences: Whites > African-Americans ($p < 0.0001$); Whites > Hispanics ($p = 0.007$). p -value to detect differences across ethnicities was calculated using Kruskal-Wallis test. Direct comparison of one ethnicity against another was done with Mann-Whitney test. Abbreviation: NT-proBNP; N-Terminal pro brain natriuretic peptide.

Figure 1b. Data points represent median (25th and 75th percentile) for each ethnicity.

Differences: Whites > Chinese-Americans ($p<0.0001$); Whites > African-Americans ($p<0.0001$); Whites > Hispanics ($p<0.001$); Hispanics > Chinese-Americans ($p=0.03$); Hispanics > African-Americans ($p<0.0001$).

p -value to detect differences across ethnicities was calculated using Kruskal-Wallis test.

Direct comparison of one ethnicity against another was done with Mann-Whitney test.

Abbreviation: NT-proBNP; N-Terminal pro brain natriuretic peptide.

Table 1

Characteristics of study participants according to early menopausal status

Characteristics	Early menopause present	Early menopause absent	<i>p</i> -value
	n = 561	n = 1714	
Age, years	65.0 ± 10.1	65.0 ± 8.9	0.90
Ethnicity			<0.0001
- Whites, %	33.5	41.5	
- Chinese-Americans, %	6.8	14.4	
- African-Americans, %	33.2	21.4	
- Hispanics, %	26.6	22.6	
> High school education, %	52.6	56.5	0.11
Cigarette smoking			0.002
- Never, %	55.7	61.2	
- Former, %	30.3	29.8	
- Current, %	14.0	9.0	
Left ventricular hypertrophy by ECG, %	0.54	0.88	0.43
Hormone therapy (current user), %	34.1	32.1	0.38
Hypertension, %	52.8	49.7	0.20
Diabetes, %	15.4	11.7	0.02
High density lipoprotein cholesterol, mg/dl	56.2 ± 15.2	56.8 ± 15.4	0.46
Interleukin-6, * pg/ml	1.4 ± 1.9	1.3 ± 1.9	0.01
eGFRcr, ml/min/1.73 m ²	75.7 ± 16.8	75.0 ± 15.8	0.40
Body mass index, kg/m ²	29.3 ± 6.2	28.3 ± 5.8	0.0005
NT-pro brain natriuretic peptide, * pg/ml	78.7 ± 2.9	74.9 ± 2.8	0.33

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

* Values are geometric mean of interleukin-6, and NT-pro brain natriuretic peptide.

Abbreviations: ECG, electrocardiogram; eGFRcr, creatinine-based estimated glomerular filtration rate.

Table 2

Percentage differences in NT-pro brain natriuretic peptide (NT-proBNP) levels associated with early menopause in postmenopausal women at MESA baseline

	Early Menopause	<i>p</i>-value	Age at Menopause	<i>p</i>-value
Model 1	7.2% (−2.0–17.2%)	0.13	−0.6% (−1.2–[−0.02]%)	0.04
Model 2	10.6% (1.3–20.7%)	0.02	−0.8% (−1.4–[−0.2]%)	0.01
Model 3	10.6% (1.7–20.3%)	0.02	−0.7% (−1.3–[−0.2]%)	0.01
Model 4	10.7% (1.7–20.4%)	0.02	−0.7% (−1.3–[−0.2]%)	0.01
Model 5	11.1% (0.6–22.7%)	0.04	−0.8% (−1.4–[−0.1]%)	0.02

Early menopause was present if menopause occurred before 45 years. There were 2275 postmenopausal women and 561 of them had early menopause. NT-proBNP was measured in pg/ml.

Model 1: Adjusted for age and body mass index

Model 2: Model 1, adjusted for ethnicity

Model 3: Model 2, adjusted for cigarette smoking, educational status, diabetes mellitus, high density lipoprotein-cholesterol, glomerular filtration rate (estimated from creatinine), interleukin-6, systolic blood pressure, diastolic blood pressure, antihypertensive medication use

Model 4: Model 3, adjusted for LVH by electrocardiogram

Model 5: Model 4, LVH replaced with left ventricular mass by MRI. 1645 postmenopausal women had MRI at baseline and 394 of them had early menopause.

* Comparisons are made to women without early menopause at MESA baseline

Abbreviations: LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging

Table 3

Percentage differences in NT-pro brain natriuretic peptide (NT-proBNP) levels associated with early menopause in postmenopausal women aged 65 years or younger at MESA baseline

	Early Menopause	<i>p</i> -value	Age at Menopause	<i>p</i> -value
Model 1	10.4% (−3.4–26.1%)	0.15	−0.8% (−1.7–0.1%)	0.10
Model 2	15.2% (1.0–31.4%)	0.04	−1.1% (−2.0–[−0.2]%)	0.02
Model 3	18.9% (4.7–34.9%)	0.008	−1.4 (−2.2–[−0.5]%)	0.003
Model 4	19.3% (5.0–35.5%)	0.007	−1.4% (−2.3–[−0.5]%)	0.003
Model 5	23.4% (6.8–42.7%)	0.005	−1.7% (−2.7–[−0.6]%)	0.002

Early menopause was present if menopause occurred before 45 years. 1166 postmenopausal women were aged 65 years or younger at baseline and 278 of them had early menopause. NT-proBNP was measured in pg/ml.

Model 1: Adjusted for age and body mass index

Model 2: Model 1, adjusted for ethnicity

Model 3: Model 2, adjusted for cigarette smoking, educational status, diabetes mellitus, high density lipoprotein-cholesterol, glomerular filtration rate (estimated from creatinine), interleukin-6, systolic blood pressure, diastolic blood pressure, antihypertensive medication use

Model 4: Model 3, adjusted for LVH by electrocardiogram

Model 4: Model 4, LVH replaced with left ventricular mass by MRI. 888 postmenopausal women aged 65 years or younger had MRI at baseline and 209 of them had early menopause.

* Comparisons are made to women without early menopause at MESA baseline

Abbreviations: LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging