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Age of Natural Menopause and Atrial Fibrillation: the Framingham Heart Study

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Abstract

Background—Early menopausal age is associated with risk of cardiovascular events including myocardial infraction, stroke, and increased mortality. Relations between menopausal age and atrial fibrillation (AF) have not been investigated. We examined the association between menopausal age and AF.

Methods—Framingham Heart Study women ≥60 years without prevalent AF and natural menopause were followed for 10 years or until incident AF. Menopausal age was modeled as a continuous variable and by categories (<45, 45–53, and >53 years). We used Cox proportional hazards regression to determine associations between menopausal age and AF risk.

Results—In 1,809 Framingham women (2,662 person-examinations, mean baseline age 71.4±7.6 years, menopausal age 49.8±3.6 years) there were 273 unique participants with incident AF. We did not identify a significant association between the standard deviation (SD) of menopausal age (3.6 years) and AF (hazard ratio [HR] per SD, 0.94; 95% CI, 0.83 to 1.06; P=0.29). In a multivariable model with established risk factors for AF, menopausal age was not associated with

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incident AF (HR per SD, 0.97; 95% CI, 0.86 to 1.09; *P*=0.60). Examining categorical menopausal age, earlier menopausal age (<45 years) was not significantly associated with increased AF risk compared to older menopausal age>53 (HR, 1.20; 95% CI, 0.74 to 1.94; *P*=0.52) or menopausal age 45–53 years (HR, 1.38; 95% CI, 0.93 to 2.04; *P*=0.11).

Conclusion—In our moderate sized, community-based sample, we did not identify menopausal age as significantly increasing AF risk. However, future larger studies will need to examine whether there is a small effect of menopausal age on AF risk.

Keywords

epidemiology; atrial fibrillation; risk factors; menopause; women

Introduction

Younger age at menopause has been associated with increased risk of myocardial infarction, stroke, and mortality.[1;2] In the Nurse's Health Study menopausal age <40 years and early menopause (age 40–44) were associated with up to 1.5- and 1.4-fold increased risk of cardiovascular events compared to menopause ≥55 years.[3] Conversely, older menopausal age (≥53 years) has been related to decreased mortality secondary to ischemic heart disease.[4] Prospective cohort studies have further related earlier age of menopause to increased risk for all-cause mortality.[2;5;6]

Given the association between menopausal age and cardiovascular events, we sought to examine the relation between age of menopause and atrial fibrillation (AF). AF has profound social and medical burdens, increasing mortality and eliminating the survival advantage that women have over men.[7] Identifying risk factors for AF in women therefore has significant public health importance.[8] To our knowledge the association between atrial fibrillation (AF) and age of menopause has had limited investigation. We considered that the myriad endocrinologic and vascular changes accompanying menopause would predispose women towards increased AF risk. We consequently hypothesized an increased risk of AF for women experiencing menopause at a younger age, and in particular, that cardiac events may mediate the increased risk for developing AF.

Methods

Study Sample

The Framingham Heart Study is a longitudinal, community-based study designed to investigate cardiovascular disease and its risk factors.[9] Original Cohort participants were enrolled in the Framingham Heart Study starting in 1948 and attend examinations every two years. Offspring Cohort participation started in 1971 and consists of examinations every four to eight years. In order to have 10 year follow-up, the present study employed data from women attending Original Cohort examination cycles 11 (1968–1971), 17 (1981–1984), and 23 (1992–1996), and Offspring Cohort examination cycles 1 (1971–1975), 3 (1983–1987), and 6 (1995–1998). Participants were included in the present analysis when they reached 60 years of age or older. Age 60 was used as the minimum age as women were expected to have reached menopause by that age. Before exclusions the sample was comprised of 4,159 participant examinations. Participants were excluded if they had prevalent AF (n=180), i.e. been diagnosed with AF prior to study entry at age 60 years; unreliable age of natural menopause secondary to oophorectomy with or without hysterectomy (n=1,190); unknown age of menopause (n=1); menopausal age<40 years (deemed premature ovarian failure,[10] n=39); estrogen use prior to menstrual cessation (n=17); or lacked complete data on key AF risk factors (n=70).

We used cross-sectional pooling to construct the dataset consistent with previous Framingham Heart Study analyses of AF,[11] such that study participants without incident AF included in the analysis were eligible to re-enter the analysis for subsequent 10-year intervals. Study participants were followed prospectively for incident AF for a maximum duration of ten years after each baseline exam. Participants provided written informed consent at each exam. Study protocols and all examination cycles were approved by the Institutional Review Board of the Boston University Medical Center.

Clinical assessments

Participants underwent a physician-administered medical interview, history, and examination at each Framingham Heart Study exam.[12] Body mass index was calculated from weight in kilograms divided by height in meters squared and systolic blood pressure as the mean of two seated measurements obtained during a standardized examination. Hypertension treatment was established by self-report of prescribed medications. Heart murmurs of clinical significance were scored as at least grade three of six systolic or any diastolic murmur recorded by a Framingham Heart Study physician at the standardized examination. The electrocardiographic PR interval was calculated from the 12-lead resting ECG as previously described.[13] Heart failure was adjudicated by three Framingham Heart Study physicians according to established major and minor criteria.[14] Covariates were selected for inclusion in the present analysis from a previously published AF risk prediction model.[11] AF was determined by presence of atrial fibrillation or atrial flutter on electrocardiographic or Holter monitoring obtained at a Framingham Heart Study examination, external clinician visit, or during hospitalization, and all available outside visits to clinicians for cardiovascular diagnoses. Incident AF was adjudicated by at least two Framingham Heart Study cardiologists.

Age of menopause

Age of natural menopause was established by a standardized, physician-administered interview at each examination. Women were queried about their menstrual status, whether periods had stopped for 1 year or more; age periods stopped, cause, defined as natural, surgical or other; history of gynecologic surgery (hysterectomy and oophorectomy, including number of ovaries removed); and use of hormone replacement therapies. Natural menopause was defined as the natural cessation of menses for ≥1 year. Menopausal age was categorized as age<45, 45–53, and >53 years of age after examining the distribution of menopausal age in a prior Framingham Heart Study analysis.[15] Women with a history of surgical cessation of menstrual periods were excluded because of lack of reliability of ascertaining menopausal age, consistent with prior Framingham Heart Study analyses of menopausal age as an exposure for cardiovascular outcomes.[16]

Statistical analyses

We summarized continuous variables with means, standard deviations, medians and interquartile ranges and examined distributions graphically. Distributions of categorical variables were examined by frequency. Menopausal age was modeled as a continuous measure (in years) and using categories defined by age cut-points: <45, 45–53, and >53 years. AF incidence rates were determined by determining the number of events per menopausal age category per 1000-person years. The association between the standard deviation of menopausal age and incident AF was determined by Cox proportional hazards regression analysis with censoring at 10 years. Models were adjusted for risk factors associated with AF, including body mass index, systolic blood pressure, hypertension treatment, PR interval, significant murmur and prevalent heart failure. Age was not included in the model because of its collinearity with age of menopause. Risk factors were measured for participants entering each 10-year risk assessment at the baseline exam. We then

constructed cumulative incidence curves using menopausal age as a categorical variable. A two-sided P-value of <0.05 was considered statistically significant and all analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

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Results

The study cohort consisted of 1,809 unique Framingham Heart Study participants with 2,662 examinations. The mean age was 71.4±7.6 years, and the mean age at natural menopause was 49.8±3.6 years (Table I). There were 273 incident AF events in follow-up. The unadjusted incidence rates per 1000 person-years were 15.8 in the menopausal age <45 category, compared to 11.5 and 13.3 in the menopausal age 45–53 and >53 years categories (Table II; P=0.24 between different age categories).

When examining menopausal age as a continuous variable, we did not observe a statistically significant association between menopausal age and risk of incident AF (P=0.29). Similarly, when examining menopausal age categories, earlier menopausal age (<45) was not associated with increased AF risk compared to older menopausal age>53 (P=0.52) or when compared to menopausal age 45–53 years (P=0.11). In multivariable analysis incorporating established risk factors for AF, age of menopause was not significantly associated with incident AF in the above analyses (Table III).

The cumulative incidence curves demonstrated no significant differences in incident AF across the three categories of menopausal age over 10-year follow-up (Figure). The log-rank test as well did not reach statistical significance (P=0.24).

Following the above results, we conducted an analysis to determine the effect size that we were powered to detect. Assuming 80% power and given our number of observed AF events, we would have required a hazard ratio of 0.84 in order to observe a significant association between increasing menopausal age and decreased risk of incident AF. In contrast, our observed hazard ratio was 0.93.

Discussion

We hypothesized an association between menopausal age and 10-year risk of incident AF in a prospective, community-based cohort, and specifically that decreased age of menopause would result in increased incident AF risk. Our hypothesis stemmed from the established association between earlier menopausal age and augmented risk for cardiovascular events.

A second rationale was the cardiovascular adaptation and remodeling by complex vascular and endocrinologic pathways resulting from menopause.[17] Aging and cardiovascular adaptation following menopause are multifactorial processes that in turn yield an increased burden of clinical risk factors associated with AF. Hypertension increases in prevalence as women age,[18] is common across ethnic and racial groups[19;20] and is a chief risk factor for

AF in community-based studies.[21;22] Hypertension has been associated with increased left ventricular hypertrophy and mass in postmenopausal women[23] and increases risk for heart failure.[24] Both hypertension and heart failure are associated with AF.[25] Obesity has risen in prevalence in adults and in the most recent National Health and Nutrition Examination Survey 33.6% of women age ≥60 years had a mean body mass index ≥30 kg/m^2.[26] Menopause results in redistribution of fat depots,[27] including epicardial fat,[28] which has been demonstrated as associated with increased risk for AF.[29] The interaction of such diverse anthropometric and clinical factors with AF risk in postmenopausal women merits continued investigation.

The final rationale for our hypothesis was the association between menopause and risk factors for AF. Inflammatory markers (e.g. C-reactive protein) are associated with increased risk of cardiovascular events in women,[30–32] have been related to menopausal status,[33] and similarly have been associated with AF.[34] Post-menopausal hematologic changes include increased hematocrit, greater plasma viscosity, and higher fibrinogen levels, which may enhance risk for cardiovascular disease and AF;[35] in the Women's Health Study fibrinogen has recently been associated with increased AF risk.[36]

Sex-specific differences in the incidence of AF and cardiac arrhythmias are well described,[37;38] and epidemiologic data have observed that AF is less prevalent in women than men.[39] Incident AF, in general, occurs at an older age in women than men.[21] Sex differences in atrial electrophysiology are demonstrated by decreased P wave indices– a noninvasive assessment of atrial electrophysiologic function – in women compared to men.[40] The study of sex-specific electrophysiologic differences from hormonal influences, specifically estrogen, is on-going. Estrogen receptors have been studied in animal and human cardiac structures.[41;42] Mice receiving ovariectomies had decreased atrioventricular nodal conduction, as measured by PR and AH intervals, compared to those receiving estrogen or intact animals.[43] In human studies, there is age-associated methylation of the estrogen receptor gene alpha in atrial tissue, suggesting down regulation of estrogen receptor expression.[44] Modeling of cellular differences in cardiac repolarization has demonstrated female cells having increased potential for arrhythmogenic early afterdepolarizations compared to male cells.[45]

Further studies are necessary to assess other cardiovascular markers (e.g. natriuretic peptides, left atrial parameters, P wave indices), their association with menopausal age, and if they modify AF risk in postmenopausal women. Remaining questions concern estrogen exposure, receptor activity, and modification of atrial electrophysiology across the spectrum of menopause.

Our study has multiple strengths. It was conducted in a community-based cohort with routine examinations occurring every two to eight years. Such frequent contact provided an opportunity for longitudinal assessments and facilitated the cross-sectional pooling employed in this study. We included participants only ≥60 years of age, thereby verifying that all participants had achieved menopause, and facilitating follow-up in older age when participants were at increased risk for incident AF. Participants with menopausal age <40 were excluded because of concern for premature ovarian failure. Additionally, the Framingham Heart Study's routine collection of varied medical and clinical records yielded the identification of incident AF.

The present study has several limitations. Framingham Heart Study participants were mostly older and primarily of European descent; the generalizability of our findings to younger women and other races and ethnicities is unknown, particularly given racial differences in AF incidence.[46;47] A chief limitation is our lack of power given our sample size and number

of incident events. A larger cohort may have a greater number of events, thereby obtaining higher power and the ability to determine smaller risks between menopausal age and incident AF. In fact, we determined that our study would have required approximately 1400 events in order for the hazard ratio of 0.93 to reach statistical significance. Furthermore, we did not examine post-menopausal hormone replacement therapy and its potential effects on AF risk. Inclusion of hormone use will be essential for larger studies exploring the association between menopause and AF. Our results may further suffer from recall bias in reporting age of natural menopause. However, as we recorded age of menopause prior to the development of AF, such recall bias is unlikely to be biased by occurrence of AF. Such random misclassification would have biased our results towards the null. It is also possible that women had unrecognized episodes of paroxysmal AF, resulting in misclassification of outcome status. More extensive rhythm monitoring, challenging in a community-based study, would be necessary to capture paroxysmal AF.

To our knowledge, the present study is the first to examine the relation between menopausal age and incident AF. Whereas we did not observe a significant association between menopausal age and AF risk, studies in larger cohorts may have increased power to explore such a potential association. AF carries tremendous social and medical burdens and the number of older adults in the U.S. continues to increase. Identification of novel risk factors will serve public health efforts by enhancing risk stratification and prevention initiatives.

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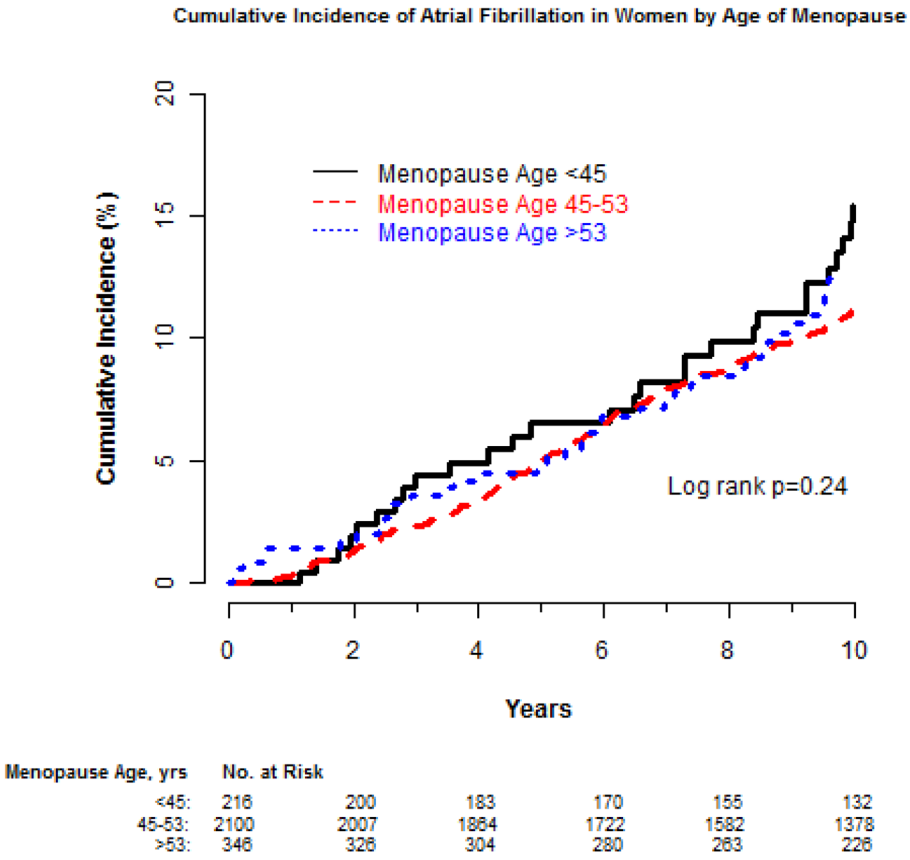

Figure.

The figure shows the cumulative incidence of atrial fibrillation, stratified by three categories of menopausal age: age<45; age 45–53; and age >53 years. The log-rank test shows no significant difference between the three curves (*P*=0.24).

Table I

Characteristics of 2,662[*] participant examinations included in the analysis.

Variable[†]	Characteristic
Age (years)	71.4 ± 7.6
Age of menopause (years)	49.8 ± 3.6
Body mass index (kg/m^2)	25.9 ± 4.9
Systolic blood pressure (mm Hg)	142 ± 22
Hypertension treatment	447 (17)
PR interval duration (msec)	164 ± 25
Significant murmur[‡]	142 (5.3)
Heart failure	51 (1.9)

[*] The 2,662 baseline examinations correspond to pooled examinations from 1,829 unique individuals.

[†] Data presented as mean ± standard deviation, or n (%).

[‡] Significant murmur defined as grade 3 out of 6 systolic or any diastolic murmur.

Table II

Incidence of atrial fibrillation from 2,662* participant examinations in eligible Framingham Heart Study women.

	Total events	Incidence rate per 1000 person-years (95% CI)
Menopausal age (years) by category		
Age <45 (n=235)	28	15.8 (9.9 – 21.7)
Age 45–53 (n=2246)	206	11.5 (9.9 – 13.1)
Age >53 (n=366)	39	13.3 (9.1 – 17.5)
Total	273	12.1 (10.7 – 13.5)

*The 2,662 baseline examinations correspond to pooled examinations from 1,809 unique individuals.

Table III

Relation of age at menopause to 10 year risk of atrial fibrillation.

Variable	Hazard Ratio	95% CI	*P*
Per standard deviation of menopausal age			
Menopausal age	0.94	0.83 – 1.06	0.29
Multivariable-adjusted‡	0.97	0.86 – 1.09	0.60
Early Menopause (<45) v. Late Menopause (>53)			
Menopausal age	1.20	0.74 – 1.94	0.52
Multivariable-adjusted	1.05	0.64 – 1.73	0.84
Early Menopause (<45) v. Mid Menopause (45 to 53)			
Menopausal age	1.38	0.93 – 2.04	0.11
Multivariable-adjusted	1.15	0.76 – 1.72	0.51

*The 2,662 baseline examinations correspond to pooled examinations from 1,809 unique individuals.

‡The multivariable covariates are body mass index, hypertension, cardiac murmur, prevalent heart failure, and PR interval.