Age at Natural Menopause and Risk of Ischemic Stroke

The Framingham Heart Study

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Background and Purpose—Women have increased lifetime stroke risk and more disabling strokes compared with men. Insights into the association between menopause and stroke could lead to new prevention strategies for women. The objective of this study was to examine the association of age at natural menopause with ischemic stroke risk in the Framingham Heart Study.

Methods—Participants included women who survived stroke-free until age 60, experienced natural menopause, did not use estrogen before menopause, and who had complete data (n=1430). Participants were followed until first ischemic stroke, death, or end of follow-up (2006). Age at natural menopause was self-reported. Cox proportional hazards models were used to examine the association between age at natural menopause (<42, 42 to 54, ≥55) and ischemic stroke risk adjusted for age, systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease and estrogen use.

Results—There were 234 ischemic strokes identified. Average age at menopause was 49 years (SD=4). Women with menopause at ages 42 to 54 (hazard ratio=0.50; 95% CI: 0.29 to 0.89) and at ages ≥55 (hazard ratio=0.31; 95% CI: 0.13 to 0.76) had lower stroke risk compared with those with menopause <42 years adjusted for covariates. Women with menopause before age 42 had twice the stroke risk compared to all other women (hazard ratio=2.03; 95% CI: 1.16 to 3.56).

Conclusion—In this prospective study, age at natural menopause before age 42 was associated with increased ischemic stroke risk. Future stroke studies with measures of endogenous hormones are needed to inform the underlying mechanisms so that novel prevention strategies for midlife women can be considered. (Stroke. 2009;40:00-00.)

Key Words: stroke ■ cerebrovascular disease ■ women ■ menopause ■ bone mineral density

Average life expectancy for women in the United States is 80 years, 5 years longer than that of men.1 Although men have an increased stroke risk, more women than men will experience a stroke during their lifetime because of their increased life span.2 Studies consistently show that women are more functionally impaired after stroke and are less likely to receive tissue plasminogen activator compared with men.3

Given the increased stroke burden and barriers to acute stroke therapy in women, it is critical to understand risk factors unique to women so that new strategies for stroke prevention can be considered.

Results from a meta-analysis demonstrated that menopause before age 50 was associated with a 25% increased risk of cardiovascular disease.4 Three of the 12 studies in the meta-analysis included stroke,5-7 with only 1 focused on incident stroke versus stroke mortality.7 This investigation from the Nurse’s Health Study failed to find an association between age at natural menopause and stroke risk; however, a protective effect of older age at menopause and ischemic stroke risk was suggested.8 With the exception of this study, prospective data on the association of age at natural menopause and stroke risk among US women are lacking.

Beyond age at natural menopause, duration of ovarian activity may be a marker of stroke risk. A recent case-control study found that a longer lifetime estrogen exposure, defined as the difference between age at menopause and age at menarche, was associated with decreased stroke risk.8 An alternative measure of cumulative endogenous estrogen exposure is bone mineral density (BMD). BMD is associated with age at menarche,9,10 age at menopause,11,12 and endogenous estrogen levels among peri- and postmenopausal women.13,14

Data from one prospective US study of elderly women demonstrated a strong association between low BMD and risk of incident stroke,15 whereas data from Third National Health and Nutrition Examination Survey I—Epidemiological Follow-up Study (NHANES I) failed to find an association.16 Further investigation of the relationship between BMD and stroke incidence is warranted.

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The primary objective of this study was to prospectively examine the association of age at natural menopause with risk of ischemic stroke in the Framingham Heart Study (FHS). A secondary objective was to examine the association of BMD and risk of ischemic stroke. Analyses were limited to ischemic stroke given the purported role of estrogen deficiency in promoting atherosclerosis.

Methods
FHS is an ongoing prospective cohort study of 5209 participants (2873 women, ages 28 to 62 at the time of enrollment) that began in 1948 in the town of Framingham, Mass. Participants undergo biennial examinations including medical histories, physical examinations, laboratory tests for vascular risk factors, and, at some examinations, brain imaging studies. Details of the study methods have been published.18

This study investigated the association of age at natural menopause and incident ischemic stroke after age 60. Among the 2873 women in the original cohort, there were 2461 who attended an examination within 3 years of age 60; this examination was designated the participant’s baseline. Participants were excluded if they had no information on age at menopause (n=7), surgical menopause or menopause of unknown cause (n=702), prevalent ischemic stroke at entry (n=18), no follow-up after entry (n=11), estrogen use before menopause (n=26), or missing risk factor data (n=267). The remaining 1430 participants comprised the study sample for the analysis of the association of age at natural menopause with risk of ischemic stroke (primary objective).

Of the 2873 women in the original cohort, 866 were alive and attended examination 20 (1986–1990), when BMD was measured; this examination was designated the participant’s baseline for the analysis of BMD and risk of ischemic stroke (secondary objective). Participants were excluded from this analysis if they had prevalent ischemic stroke at entry (n=43) or no follow-up after entry (n=7). Of the remaining 816, BMD was measured in 654 women. These women comprised the study sample for the secondary objective. All participants provided written informed consent, and the study was approved by the Boston Medical Center Institutional Review Board.

Baseline Covariates
Baseline covariates were assessed at age 60 (±3 years) for the primary objective and at the time of BMD measurement for the secondary objective. The following covariates were considered: systolic blood pressure, diabetes, atrial fibrillation, cardiovascular disease, current smoking status, body mass index, and estrogen use. Systolic blood pressure was recorded as the average of 2 physician-recorded measurements. Diabetes was defined as a random blood glucose ≥200 mg/dL, previous diagnosis or treatment with diabetes medication (insulin or oral hypoglycemia agent). Prior cardiovascular disease included coronary heart disease, congestive heart failure and intermittent claudication. Atrial fibrillation was obtained from a standard 12-lead ECG completed at or before the baseline examination. Estrogen use was defined as someone taking estrogen at their baseline assessment. Women taking estrogen before menopause were excluded from the analysis so this covariate measured estrogen started after menopause. Analyses were limited to those with complete covariate data.

Stroke Ascertainment
The primary outcome was incident ischemic stroke. Stroke was defined clinically as a focal neurological deficit of sudden or rapid onset that persisted for more than 24 hours. Continuous surveillance for cerebrovascular events included daily hospital monitoring, tracking of medical encounters, and examination of those with possible stroke symptoms identified at routine biennial examinations. Events were adjudicated by at least 2 neurologists, and with verification of stroke by imaging when available. Stroke occurrence and characteristics, including subtypes, were determined at the end of the acute stroke phase according to uniform criteria and a standardized protocol.18,19

Age at Natural Menopause
At each biennial examination, women were queried as to whether periods had stopped for 1 year or more, the age at which periods ceased, the cause of stopped periods (natural, surgical, other), whether a hysterectomy was performed, and number of ovaries removed. Natural menopause occurred if a woman had ceased menstruating naturally for at least 1 year. Age at natural menopause was retrospectively assigned as the self-reported age at last menstrual period.

Bone Mineral Density
BMDs of the femur (neck and trochanter) and distal third of the radius were measured in members of the cohort who came for their 20th biennial examination in 1986 to 1990. Measurements were done using dual-photon absorptiometry for the hip (DP3; Lunar Corp, Madison, Wisc) and single-photon absorptiometry for the distal third of the radius (LUNAR SP2; Lunar Corp).

Statistical Analysis
Baseline characteristics were calculated using frequencies and percentages or means and standard deviations (SD). Cox proportional hazards models were used to examine the association between age at natural menopause and risk of ischemic stroke. Individuals were censored at death, hemorrhagic stroke, last examination or contact date, or end of follow-up (December 2006). Survival age was used as the outcome in all models, with entry age used as the left truncation limit. Given an observed nonlinear relationship, age at natural menopause was modeled categorically (<42 [referent], 42 to 54, ≥55). Models were run age-adjusted and adjusted for age plus baseline covariates (systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease, estrogen use). All covariates were modeled dichotomously with the exception of systolic blood pressure and age which were modeled continuously. A Wald χ² test was used to test the overall association between age at natural menopause and risk of stroke in the adjusted model. Models were also run limited to never smokers and never estrogen users given the potential confounding effects of these covariates.

Cox proportional hazards models were used to examine the association between BMD and risk of ischemic stroke, with individuals censored as described above. Survival age was again used as the outcome in all models, with age at the 20th examination used as the left truncation limit. Models were run separately for each BMD site. BMD was modeled categorically based on quintiles of the distribution of BMD at each site with the middle quintile as the referent. BMD quintiles were determined within age groups (67 to 69, 70 to 74, 75 to 79, ≥80). Models were run age-adjusted and adjusted for the covariates described above with additional adjustment for body mass index. Using the adjusted models, Wald χ² tests were used to test the overall associations of BMD at each site and risk of stroke. Models were also run limited to those not taking antihypertensives given the potential confounding effects of this covariate.

Results
For the primary objective, there were 1430 women with complete data. Baseline covariate data for these women is included in Table 1. Average age at menopause was 49 years (SD=4). Women were followed for an average of 22 years (SD=9). There were 234 incident ischemic strokes occurring at an average age of 80 years (SD=9). The Figure displays cumulative incidence of ischemic stroke by age and age at natural menopause, and Table 2 displays the model results. In the age-adjusted model, women with menopause at ages 42 to 54 (hazard ratio [HR]=0.57; 95% CI: 0.33 to 1.01) and at ages ≥55 (HR=0.33; 95% CI: 0.14 to 0.79) had lower stroke risk compared with those with menopause <42 years. These associations were relatively unchanged with adjustment for baseline covariates. In the adjusted model, there was a
significant overall association between age at natural menopause and ischemic stroke risk ($P=0.02$). Women with menopause before age 42 had twice the risk of ischemic stroke compared to all other women (HR=2.03; 95% CI: 1.16 to 3.56). Limiting to never smokers or to never estrogen users, results were similar (Table 2).

Six hundred fifty-four women had at least one BMD measurement with an average age at measurement of 76 years (SD=5). Women were followed an average of 12 years (SD=5). In this subset, there were 92 ischemic strokes. Table 3 displays the model results. Cut-points for defining quintiles of BMD are provided in supplemental Table I, available online at http://stroke.ahajournals.org. In adjusted models, there were borderline significant associations with BMD at the trochanter ($P=0.07$) and radius ($P=0.07$) and ischemic stroke risk. For BMD measured at the trochanter, a U-shaped pattern in risk was observed with women in the lowest (HR=2.36, 95% CI: 1.15 to 4.83) and highest (HR=1.94, 95% CI: 0.94 to 3.95) quintiles of BMD having elevated stroke risk compared with women in the middle quintile. A similar pattern was observed at the radius (Q1–HR=2.92, 95% CI: 1.55 to 6.34; Q5–HR=2.34, 95% CI: 1.12 to 5.30). Limiting the analysis to those not using antihypertensives, results were similar (data not shown).

**Discussion**

In this prospective study, we observed a significant association between age at natural menopause and ischemic stroke risk in a cohort of women followed from age 60. This association was nonlinear and reflected an increased risk of ischemic stroke in those with natural menopause before 42. Menopause at ≤40 years is termed premature ovarian failure (POF). The etiology of POF is unknown, although POF is thought to arise from different processes than those leading to natural menopause around age 50. Prevalence of POF is 1% to 2% among women, with an additional 3% to 10% of women experiencing “early” menopause defined as natural menopause before age 45.20,21 Although women with menopause before 42 years represent a small subgroup of the total population, data from this study suggest that 4% to 5% of strokes in all women can be attributed to this risk factor. Reasons for increased ischemic stroke risk among women with POF or early menopause are not clear but early loss of ovarian function coupled with a prolonged low estrogen state is a plausible hypothesis.

The menopausal transition represents a change in endogenous hormones including decreasing estradiol levels several years before menopause and relative estrogen deficiency within 2 to 3 years of the final menstrual period.22 Estrogen deficiency is thought to promote cardiovascular disease,23 perhaps through functional or structural changes in the arteries,24 and as such early onset of estrogen loss in women with POF may contribute to increased stroke risk. However, the role of estrogen deficiency has become controversial in

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**Table 1. Baseline Characteristics (percent or mean±SD) at Age 60 Among Women in the Framingham Heart Study (n=1430)**

<table>
<thead>
<tr>
<th>Baseline covariate</th>
<th>Age, years 60.0±0.8</th>
<th>Systolic blood pressure, mm Hg 141±24</th>
<th>History of diabetes 4%</th>
<th>History of CVD 7%</th>
<th>History of AF 1%</th>
<th>Current smoking 32%</th>
<th>Hormone replacement therapy 19%</th>
<th>BMI, kg/m² 27±5</th>
</tr>
</thead>
</table>

CVD indicates cardiovascular disease; AF, atrial fibrillation; BMI, body mass index.

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**Figure.** Cumulative incidence of ischemic stroke by age and age at natural menopause among women in the Framingham Heart Study (n=1430).
light of the higher stroke risk associated with hormone replacement therapy (HRT) in clinical trials. Recent analyses of Women’s Health Initiative (WHI) randomized controlled trial data suggest that the timing of HRT initiation may modify the association of HRT and cardiovascular risk, with the effects of HRT being favorable in women initiating therapy in close proximity to menopause. Interestingly, this pattern does not hold for stroke, further complicating an understanding of the hormone-stroke association.

Table 2. Associations of Age at Natural Menopause and Risk of Incident Ischemic Stroke Among Women in the Framingham Heart Study (n=1430)

<table>
<thead>
<tr>
<th>Age at natural menopause</th>
<th>No. of Participants</th>
<th>No. of Ischemic Strokes</th>
<th>Age-Adjusted HR 95% CI P</th>
<th>Multivariable-Adjusted* HR 95% CI P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;42</td>
<td>56</td>
<td>13</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>42–54</td>
<td>1299</td>
<td>213</td>
<td>0.57 0.33–1.01 0.05</td>
<td>0.50 0.29–0.89 0.02</td>
</tr>
<tr>
<td>≥55</td>
<td>75</td>
<td>8</td>
<td>0.33 0.14–0.79 0.01</td>
<td>0.31 0.13–0.76 0.01</td>
</tr>
<tr>
<td>Never smokers at age 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;42</td>
<td>30</td>
<td>9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>42–54</td>
<td>605</td>
<td>96</td>
<td>0.38 0.19–0.76 0.01</td>
<td>0.39 0.20–0.78 0.01</td>
</tr>
<tr>
<td>≥55</td>
<td>40</td>
<td>6</td>
<td>0.34 0.12–0.96 0.04</td>
<td>0.40 0.14–1.12 0.08</td>
</tr>
<tr>
<td>Never estrogen users at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;42</td>
<td>51</td>
<td>12</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>42–54</td>
<td>1138</td>
<td>193</td>
<td>0.54 0.30–0.97 0.04</td>
<td>0.48 0.27–0.87 0.02</td>
</tr>
<tr>
<td>≥55</td>
<td>63</td>
<td>7</td>
<td>0.31 0.12–0.79 0.01</td>
<td>0.30 0.12–0.77 0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease, and estrogen use.

Table 3. Associations of Bone Mineral Density Measured at 3 Sites and Risk of Incident Ischemic Stroke Among Women in the Framingham Heart Study (n=654)

<table>
<thead>
<tr>
<th>Quintile of BMD</th>
<th>No. of Participants</th>
<th>No. of Ischemic Strokes</th>
<th>Age-Adjusted HR 95% CI P</th>
<th>Multivariable-Adjusted* HR 95% CI P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>122</td>
<td>18</td>
<td>1.37 0.69–2.73 0.36</td>
<td>1.33 0.66–2.68 0.42</td>
</tr>
<tr>
<td>Q2</td>
<td>124</td>
<td>18</td>
<td>1.25 0.63–2.38 0.33</td>
<td>1.30 0.65–2.59 0.45</td>
</tr>
<tr>
<td>Q3</td>
<td>126</td>
<td>15</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Q4</td>
<td>124</td>
<td>17</td>
<td>1.18 0.59–2.36 0.65</td>
<td>0.92 0.45–1.88 0.81</td>
</tr>
<tr>
<td>Q5</td>
<td>124</td>
<td>24</td>
<td>1.72 0.90–3.29 0.10</td>
<td>1.41 0.72–2.76 0.32</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>125</td>
<td>25</td>
<td>2.17 1.07–4.38 0.03</td>
<td>2.36 1.15–4.83 0.02</td>
</tr>
<tr>
<td>Q2</td>
<td>127</td>
<td>19</td>
<td>1.13 0.51–2.52 0.76</td>
<td>1.07 0.48–2.41 0.87</td>
</tr>
<tr>
<td>Q3</td>
<td>128</td>
<td>9</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Q4</td>
<td>131</td>
<td>18</td>
<td>1.90 0.93–3.86 0.08</td>
<td>1.77 0.86–3.64 0.12</td>
</tr>
<tr>
<td>Q5</td>
<td>126</td>
<td>24</td>
<td>2.38 1.19–4.77 0.01</td>
<td>1.94 0.94–3.95 0.07</td>
</tr>
<tr>
<td>Radius</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>122</td>
<td>22</td>
<td>3.18 1.48–6.82 0.00</td>
<td>2.92 1.55–6.34 0.01</td>
</tr>
<tr>
<td>Q2</td>
<td>123</td>
<td>12</td>
<td>2.10 0.95–4.65 0.07</td>
<td>1.94 0.87–4.32 0.11</td>
</tr>
<tr>
<td>Q3</td>
<td>125</td>
<td>12</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Q4</td>
<td>123</td>
<td>21</td>
<td>2.07 0.93–4.60 0.08</td>
<td>1.68 0.74–3.80 0.21</td>
</tr>
<tr>
<td>Q5</td>
<td>123</td>
<td>24</td>
<td>2.92 1.36–6.28 0.01</td>
<td>2.43 1.12–5.30 0.03</td>
</tr>
</tbody>
</table>

Q indicates quintile; BMD, bone mineral density.

*Adjusted for age, systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease, estrogen use, and body mass index.
linear association of decreasing BMD and increasing stroke risk, we observed a U-shaped pattern. Women in the lowest quintiles of BMD (trochanter and radius) had elevated risk. This finding supports the estrogen deficiency-stroke hypothesis, although other explanations are possible. Bone metabolism and atherosclerosis share factors including osteopontin and osteocalcin, as well as other potential pathogenic contributors such as oxidized lipids and hypertension. This link is supported by an association between low BMD and carotid plaques. The finding of elevated stroke risk with the highest quintile of BMD is unexpected and could be real but could also be the result of misspecification of our model, residual confounding, or selection bias given the age at which BMD was measured in this study.

More research is needed to understand the impact of endogenous estrogen on stroke risk. However, given the harmful association of HRT with stroke in recent trials and negative findings of studies of endogenous estrogen and nonstroke cardiovascular disease endpoints, alternate hormonal pathways, including changes in androgens and sex-hormone binding globulin with menopause, should be explored. Lower levels of sex-hormone binding globulin (SHBG) and higher levels of free androgen index (FAI) have been associated with cardiovascular disease, but again, data on stroke are lacking. Low SHBG and high FAI were also related to an adverse cardiovascular risk factor profile, including higher insulin, glucose, lipids, and hemostatic and inflammatory markers, in a study of perimenopausal women. Estradiol was also associated with an adverse risk factor profile but to a lesser degree. These findings suggest that the association of age at menopause and stroke risk may be mediated through changes in risk factors which occur with menopause, although associations remained after adjustment for risk factors in this study. Alternatively, an adverse cardiovascular risk factor profile in premenopausal women may be associated with earlier menopause.

Some limitations warrant discussion. The population was limited to white women who were recruited in 1948; therefore, results may not be generalizable to different populations or to more recent birth cohorts. Although age at natural menopause in the Framingham population is similar to estimates in more recent cohorts, there have been temporal trends in increasing age at menopause. Oral contraceptive use and use of hormone replacement therapy were uncommon in this cohort because of the study time period limiting generalizability to more recent birth cohorts with a greater prevalence of these medications. Similarly, secular trends in stroke risk factors or their treatment may limit generalizability. Women with stroke before age 60 were excluded. Although ischemic stroke was rare before 60, if early menopause is associated with stroke at younger ages, the association of age at menopause and stroke may differ from that presented. Similarly, the secondary analysis followed women prospectively from BMD measurement, which occurred on average at 76 years. Women who experienced stroke or who died before BMD measurement were not included. This may have introduced bias and suggests that our results should be confirmed in different populations and across a broader range of ages. Although we adjusted for confounders, with a focus on factors known to influence stroke in this population, there may be other unaccounted for confounders. For example, we did not include metabolic syndrome, measures of central adiposity or parity, which may be confounders, because they were not available for this population for the time frame under study. Sample sizes and numbers of events were small in some analyses, which may have limited power. This study relied on self-reported menopausal status which may be subject to recall bias, although the prospective biennial exams minimize this possibility.

Summary

Given the increased stroke burden in women, it is critical to understand risk factors unique to women so that new strategies for prevention can be considered. Results from the current study demonstrated an elevated risk of ischemic stroke in women with early menopause and possible POF and in women with low BMD. These findings raise the hypothesis that estrogen deficiency may play a role in ischemic stroke but current evidence regarding this hypothesis is inconsistent. Alternate hypotheses, including the role of androgens and/or a common cause of BMD and stroke, are also possible. Future studies, with measures of endogenous hormones, are needed to unravel the relationship between hormonal changes that occur with menopause, either premature or at the usual onset, and ischemic stroke.

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Disclosures

None.

References

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Table I. Quintiles of Bone Mineral Density by Site and Age Group Among Women in the Framingham Heart Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Femoral neck</th>
<th>Trochanter</th>
<th>Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Range</td>
<td>Q1</td>
</tr>
<tr>
<td>67–69</td>
<td>56</td>
<td>0.498–1.062</td>
<td>0.554</td>
</tr>
<tr>
<td>70–74</td>
<td>239</td>
<td>0.182–1.164</td>
<td>0.531</td>
</tr>
<tr>
<td>75–79</td>
<td>189</td>
<td>0.475–1.027</td>
<td>0.521</td>
</tr>
<tr>
<td>80+</td>
<td>136</td>
<td>0.442–0.984</td>
<td>0.498</td>
</tr>
</tbody>
</table>

Values represent the upper end of the quintile with greater values falling to the next quintile.
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