Age at Natural Menopause and Stroke Mortality
Cohort Study With 3561 Stroke Deaths During 37-Year Follow-Up

Bjarne K. Jacobsen, PhD; Ivar Heuch, PhD; Gunnar Kvåle, MD, PhD

Background and Purpose—Young age at natural menopause has been related to increased cardiovascular mortality, but few studies have examined the relationship with stroke risk specifically.

Methods—In a cohort of 19,731 Norwegian women, we analyzed the relationship between age at natural menopause and stroke mortality. A total of 3561 women died of stroke during the 37-year follow-up from 1961 through 1997. Smoking prevalence was low in the underlying population, and use of hormone replacement therapy was very rare.

Results—No significant linear relationship was found between age at menopause and stroke mortality. A 3-year increase in age at menopause was associated with a 1.0% estimated increase in stroke mortality (95% CI, 1.5–3.6). No relationships were found for ischemic strokes (271 deaths) or hemorrhagic strokes (389 deaths) when considering the stroke deaths with sufficient information on death certificates. The estimate of the association between age at natural menopause and stroke mortality was hardly influenced by mortality in women with very early (aged <40 years) or late (aged >55 years) menopause, or by a number of possible confounding variables.

Conclusions—Age at natural menopause is essentially unrelated to stroke mortality. (Stroke. 2004;35:1548-1551.)

Key Words: epidemiology ■ menopause ■ mortality ■ stroke ■ postmenopause ■ prospective studies

One of the major hormonal changes in women’s lives is menopause. Several recent studies have indicated that women with a relatively low age at menopause have an increased risk of coronary heart disease, but few studies with more than 100 cases have examined the impact of age at natural menopause on risk of stroke. One study indicated an increased risk in women with very early menopause (aged <40 years), whereas 2 other studies did not support any relationship. Only 1 previous study, the largest, with a total of 350 incident cases of stroke, reported results for ischemic and hemorrhagic strokes separately.

We therefore investigated the relationship between age at natural menopause and stroke mortality in a Norwegian cohort including 19,731 women with 37 years of follow-up. During this period, 3561 women died, with stroke registered as the cause of death.

Subjects and Methods
Between 1956 and 1959, all women in the 3 Norwegian counties of Vestfold, Aust-Agder, and Nord-Trøndelag were invited to attend a screening program for early diagnosis of breast cancer. Each woman was interviewed according to a standardized questionnaire and had a clinical breast examination performed by a physician. Local physicians or public health nurses who had been informed about the objectives of the study in advance conducted the interviews. A total of 63,090 women aged 32 to 74 years in January 1961 were included in the study, corresponding to a response rate of 74.2%. The information collected comprised, inter alia, age at menarche and menopause (if the woman was postmenopausal), number of full-term pregnancies, and ages at first and last delivery, as well as information about surgery on reproductive organs (eg, oophorectomy). Particularly, the women were asked their age when menstruation stopped, which was recorded as age at menopause. The screening procedures have been detailed previously.

A total of 22,151 women stated their age at menopause. However, 2420 women also reported unilateral or bilateral oophorectomy, other ovarian operations, hysterectomy, or unspecified operations on the womb, leaving 19,731 women for analysis of the effects of natural menopause.

Information on height and weight was available for 13,622 of the 19,731 women, and was derived from separate measurements made during the period 1963 to 1975 as part of a compulsory mass examination for tuberculosis. Body mass index was calculated as kilograms per meter squared.

The official personal registration number served as unique identification of each woman and made it possible to link data about age at menopause to information on vital status and cause of death obtained from files kept at Statistics Norway in Oslo. Follow-up started January 1, 1961. During the complete follow-up through 1997, 3561 women died of stroke (International Classification of Diseases [ICD]-7, 331 to 334; ICD-8, 431 to 438; ICD-9, 431 to 438; ICD-10, I61-I69). Women with ischemic stroke (ICD-7, 332; ICD-8, 432 to 435; ICD-9, 432 to 435; ICD-10, I63) or hemorrhagic stroke (ICD-7, 331; ICD-8, 431; ICD-9, 431–432; ICD-10, I61–I62) were identified. Subarachnoid hemorrhages (ICD-7, 330; ICD-8, 430; ICD-9, 430; ICD-10, I60) were not included in the total number of strokes but were analyzed separately.

The relationship between age at natural menopause and stroke mortality was investigated in a Cox proportional hazard regression model using attained age (divided into 2-month periods) as the time variable. Women who were alive at the end of follow-up were...
censored on December 31, 1997, and women who emigrated were censored on the day they left Norway. In all analyses, we adjusted for birth cohort (1886 to 1889, 1890 to 1894, 1895 to 1899, 1900 to 1904, 1905 to 1909, 1910 to 1914, and 1915 to 1926), county of residence, and as an indicator of social class, occupational category (7 categories). Married housewives were assigned to the occupational class of their husbands.

In the tables, age at menopause was categorized into 7 groups: aged ≤40 years, 41 to 43, 44 to 46, 47 to 49, 50 to 52, 53 to 55, and 56 to 60. However, when computing the P value for linear trend and mean change in mortality rate related to an increase in age at menopause by 3 years, we included age at menopause in the model as a continuous (1-year interval) variable. Body mass index was adjusted for in a separate analysis restricted to women with information about height and weight and with follow-up starting January 1 of the year after the measurements were made.

We performed the analyses in 3 predetermined attained age groups (<70 years, 70 to 79 years, and ≥80 years) and within subgroups defined by demographic and reproductive variables. All analyses were performed using SAS software (SAS Institute).

Results
The mean and median ages at natural menopause in the women in our analysis were 48.4 and 49 years, respectively. The SD was 4.1 years. A total of 2.8% of the women stated they had experienced menopause before age 40, and 1.6% had menopause after age 55. Among women born before 1900 (the birth cohorts including women who were certainly postmenopausal when the interviews were conducted), the mean and median ages at menopause were 48.9 and 50 years, respectively. The mean age at start of follow-up was 61.8 (range 34 to 74) years. Nearly 13% were aged 32 to 54 years at the start of follow-up, 56% were aged 55 to 64 years, and 31% were aged 65 to 74 years. The mean follow-up period was 20.6 (range 0 to 37) years.

A total of 3561 women died during follow-up with stroke registered as the underlying cause. Table 1 shows the relationship between age at natural menopause and stroke mortality. The overall stroke mortality rate was 8.7 per 1000 person years. Although a linear association may be suggested, there was no strong or statistically significant relationship between age at natural menopause and stroke mortality. A 3-year increase in age at menopause was associated with a 1.0% increase in stroke mortality (95% CI, 0.1, 3.6). When women with very early (<40 years) or late (>55 years) menopause were excluded from the analysis, the mean percent increase in mortality associated with a 3-year increase in age at menopause was essentially unaffected (ie, 1.1% [95% CI, 0.2, 4.2]).

Analyses were also conducted within strata defined by a number of possible confounders and effect modifiers (birth cohort, county of residence, occupational category, age at menarche, parity, age at first delivery, and, in multiparous women, age at last delivery). The analyses confirmed the results from the main analysis presented in Table 1. No association could be established in any of the 3 groups for attained age (P value for heterogeneity=0.98; Table 2). Furthermore, the association between age at menopause and stroke mortality did not differ over birth cohorts (P value for heterogeneity=0.09; P value for linear trend over the birth cohorts=0.23), and the relationship between age at natural menopause and stroke mortality in women born before 1900 and women born later was essentially the same (Table 2). The data might suggest a stronger relationship with women who were >31 years when they gave birth to their first child than in women who were younger at first delivery, but no significant linear trend over categories defined by age at first delivery could be established (P=0.08; data not shown in tables).

We also performed a separate analysis with additional adjustment for age at menarche, parity, and age at first delivery. This analysis was restricted to 13 260 women with 1 or more children and with data about age at menarche and first delivery. A total of 2454 stroke deaths were recorded during follow-up. The association between age at menopause and stroke mortality was virtually unaffected by these adjustments or by further adjustments for age at last delivery.

In women with information about body mass index, we found a 1.9% (95% CI, 1.3, 5.1) increase in mortality associated with a 3-year increase in age at natural menopause. Adjustment for

| TABLE 1. Stroke Mortality According to Age at Natural Menopause |
|-------------------|-----------------|-----------------|-----------------|-----------------|
| Age at Menopause, y | No. of Women | No. of Person Years | No. of Stroke Deaths | RR (95 % CI) |
| ≤40                | 1054          | 22 954           | 157              | 0.94 (0.79, 1.11) |
| 41–43              | 1267          | 27 596           | 201              | 0.96 (0.83, 1.11) |
| 44–46              | 2823          | 60 531           | 472              | 0.99 (0.89, 1.10) |
| 47–49              | 5135          | 109 849          | 907              | 0.99 (0.91, 1.08) |
| 50–52              | 6917          | 138 382          | 1309             | 1.00 (Reference) |
| 53–55              | 2217          | 43 073           | 443              | 1.00 (0.89, 1.11) |
| 56–60              | 318           | 5368             | 72               | 1.08 (0.85, 1.37) |

Mean increase in mortality (%) = 1.0 (95% CI, 1.5, 3.6).

P value for linear trend = 0.44

RR indicates relative risk.

*Mean increase in stroke mortality (in %) associated with a 3-year increase in age at menopause (95% CI). Age at menopause included in the model as continuous (1-year interval) variable. Results are based on the Cox proportional hazards model and adjusted for attained age, county, occupational group, and birth cohort.

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>No. of Stroke Deaths</th>
<th>Mean Increase in Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1886–1899</td>
<td>2143</td>
<td>0.9 (95% CI, 2.2, 4.1)</td>
</tr>
<tr>
<td>1900–1926</td>
<td>1418</td>
<td>0.8 (95% CI, 3.6, 5.4)</td>
</tr>
</tbody>
</table>

*Mean increase in stroke mortality (in %) associated with a 3-year increase in age at menopause (95% CI). Age at menopause included in the model as continuous (1-year interval) variable. Results are based on the Cox proportional hazards model and are adjusted for attained age, county, occupational group, and birth cohort.
body mass index (in addition to the standard adjustments) did not influence the association between age at menopause and stroke mortality; the point estimate and 95% CIs were practically identical before and after adjustments.

In the majority of stroke deaths, death certificates did not indicate ischemic or hemorrhagic stroke. However, on the basis of death certificates, 389 (10.9%) of the strokes were classified as hemorrhagic and 271 (7.6%) were ischemic. There were 35 deaths associated with subarachnoid hemorrhages.

We found no definite relationship between age at natural menopause and mortality of ischemic or hemorrhagic strokes (Table 3). This was also the case when the analyses were restricted to women with information about age at menarche, parity, and age at first delivery, and when these variables were included in the statistical model. The low number of deaths attributed to subarachnoid hemorrhages precluded detailed analyses. However, no statistically significant relationship with age at natural menopause was suggested because a 3-year increase in age at menopause was associated with a 15% (95% CI, −14.54) increase in stroke mortality (P=0.36).

Discussion

The present results indicate that age at natural menopause is not related to stroke mortality. Thus, age at menopause is only very weakly, or not at all, related to stroke risk, but may be related to the risk of coronary heart disease. This may be a puzzling finding because cerebrovascular diseases and coronary heart disease share some risk factors such as hypertension (both hemorrhagic and ischemic strokes), smoking, hypercholesterolemia, and diabetes (ischemic strokes).

However, whereas evidence for a relationship between blood pressure and stroke risk is very convincing, large prospective studies indicate that there is no relationship between total serum cholesterol and overall stroke risk and that a positive relationship is found for ischemic strokes and an inverse relationship for hemorrhagic strokes. Longitudinal studies indicate that the menopausal transition does not influence the blood pressure much, whereas blood lipid levels tend to worsen. Thus, one may predict that menopause is of less importance for the overall stroke risk than the risk of coronary heart disease.

Our study has at least 2 major strengths: the large number of stroke deaths and the prospective design that makes biased reporting of age at menopause unlikely. We included more than 3500 stroke deaths, whereas the previous largest study included 350 incident cases of stroke.

Because the age at menopause was self-reported, there will be some inherent misclassification. Thus, a possible relationship may have been attenuated. The validity of the information about age at menopause is supported by the expected finding of a positive association between age at menopause and breast cancer risk in this cohort.

We based our analyses on death certificates. The likelihood of obtaining a correct stroke diagnosis must be assumed to be unrelated to age at natural menopause, and therefore, the misclassification is nondifferential and may conceal a true relationship. Thus, of particular note is finding that the relationship was independent of attained age because the cause of death diagnosis is more trustworthy in older than in younger age groups.

We found no significant difference between ischemic and hemorrhagic strokes with regard to the relationship with age at natural menopause, thereby confirming the results from the Nurses’ Health Study. Because more than half of the women died before 1981, and at a rather advanced age (median age at death was 82 years), modern diagnostic tools such as computed tomography (CT) were to a limited degree used to determine the type of stroke. A relatively low proportion (18.5%) of the strokes was specifically reported as ischemic or hemorrhagic. Still, our study contributes to the knowledge about this topic because it includes more cases of ischemic stroke and 5 times as many cases of hemorrhagic stroke than the only previous study, which analyzed the 2 types of strokes separately.

It may seem unexpected that more deaths were reported as hemorrhagic stroke than ischemic because the latter is more common in Norway. However, still today, when CT is often used (at least in the hospitals) when stroke is suspected on the basis of clinical examination, most stroke deaths in Norway are

### Table 3. Ischemic and Hemorrhagic Stroke Mortality According to Age at Natural Menopause

<table>
<thead>
<tr>
<th>Age at menopause, y</th>
<th>No. of deaths</th>
<th>RR (95 % CI)</th>
<th>No. of deaths</th>
<th>RR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>9</td>
<td>0.68 (0.33, 1.40)</td>
<td>23</td>
<td>1.26 (0.81, 1.97)</td>
</tr>
<tr>
<td>41–43</td>
<td>13</td>
<td>0.86 (0.48, 1.53)</td>
<td>17</td>
<td>0.75 (0.45, 1.25)</td>
</tr>
<tr>
<td>44–46</td>
<td>46</td>
<td>1.33 (0.94, 1.90)</td>
<td>58</td>
<td>1.13 (0.83, 1.54)</td>
</tr>
<tr>
<td>47–49</td>
<td>67</td>
<td>0.98 (0.72, 1.34)</td>
<td>93</td>
<td>0.96 (0.74, 1.25)</td>
</tr>
<tr>
<td>50–52</td>
<td>98</td>
<td>1.00 (Reference)</td>
<td>145</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>53–55</td>
<td>33</td>
<td>0.97 (0.65, 1.44)</td>
<td>45</td>
<td>0.90 (0.64, 1.26)</td>
</tr>
<tr>
<td>56–60</td>
<td>5</td>
<td>0.98 (0.40, 2.42)</td>
<td>8</td>
<td>0.95 (0.47, 1.94)</td>
</tr>
</tbody>
</table>

Mean increase in mortality (%)*

- Ischemic Strokes: 0.2 (−8.6, 9.8)
- Hemorrhagic Strokes: −2.9 (−9.9, 4.5)

*Mean increase in stroke mortality (in %) associated with a 3-year increase in age at menopause (95% CI). Age at menopause included in the model as continuous (1-year interval) variable. Results are based on the Cox proportional hazards model and adjusted for attained age, county, occupational group, and birth cohort.
not specified as ischemic or hemorrhagic on death certificates, and among those specified, the number of hemorrhagic strokes exceeds that of ischemic strokes, maybe because hemorrhagic strokes have higher acute mortality.

Many determinants have been suggested for age at menopause, including genetic factors, demographic variables (eg, never been married and low social class), and reproductive factors (eg, late menarche, nulliparity, no use of oral contraceptives), as well as behavioral variables such as smoking and body mass index. We found that high parity and high age at last delivery were associated with relatively high age at menopause in this data set, probably because the fertility was reduced in the years before menopause was evident. The consistent finding of no relationship in most of the subgroups of the women included in this study, as well as adjusted analyses, suggests that confounding by factors potentially affecting age at menopause was not a significant problem.

Smoking is the behavioral factor that has been related most consistently to early menopause because it lowers the age at menopause by 1 to 2 years. Because smoking increases the risk of particularly ischemic strokes, a weak inverse relationship between age at menopause and stroke mortality (the opposite of what we found) could therefore be attributed to confounding by smoking. Unfortunately, no information was available about smoking habits of the individual women in our study. However, as discussed in some detail previously, the majority (a minimum of 85%) of the women in the birth cohorts considered were nonsmokers when they were aged 45 to 49 years. However, the smoking prevalence increased in later birth cohorts. If smoking influenced our results, we would expect a linear interaction between birth cohort and the effect of age at menopause on stroke mortality. Such an interaction was not found in our data set.

Hormone replacement therapy could have introduced misclassification with regard to age at menopause and possible confounding. However, 99% of the women included in our analysis were born before 1912, ie, they were ≥50 years when estrogen medication for use in perimenopausal and postmenopausal years was introduced in Norway in the early 1960s. Thus, the prevalence of replacement therapy in women in the included analysis is likely very low. For similar reasons, use of oral contraceptives does not represent a relevant confounder in our analysis.

A low age at natural menopause may reflect clinical or subclinical medical conditions in some women that may influence their stroke mortality. For example, reduced age at natural menopause has been reported in women with diabetes mellitus type 2 and diabetes is an established risk factor for ischemic stroke. The relationship between age at natural menopause and stroke mortality would have tended to be inverse if diabetes or any other medical condition or behavioral factor that reduces the age at menopause and increases the risk of stroke confounded our results. Thus, the relationship between age at natural menopause and stroke mortality may be slightly more positive than we are able to demonstrate.

In summary, we find that age at natural menopause is not related to stroke mortality. However, because of nondifferential misclassification and possible confounding, a very weak positive relationship without practical importance cannot be ruled out.

Acknowledgments

The breast cancer screening program was initiated and organized by the Norwegian Cancer Society. The data about age at menopause were collected before ethics committees were established. However, the follow-up study was approved by the Norwegian Data Inspectorate, which considered the legal and ethical issues of the study.

References

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