Reproductive factors and fatal hip fractures. A Norwegian prospective study of 63 000 women

Bjarne K Jacobsen, Steinar Nilsen, Ivar Heuch, Gunnar Kvåle

Abstract

Study objective—The aim of the study was to investigate the impact of reproductive variables (age at menarche, menopause, first and last birth as well as parity, lactation, and abortions) on hip fracture mortality.

Design and setting—A prospective study in Norway with more than 60 000 women followed up for 29 years. A total of 465 deaths as a result of hip fracture were recorded.

Main results—Statistically significant linear relations (p ≤ 0.02) were found between both age at menarche and length of reproductive period (defined as age at menopause to age at menarche) and the mortality of hip fractures in women aged less than 80. The death rate for women with a late menarche (≥17 years) was twice that of the women with relatively early menarche (≤13 years). Compared with women with less than 30 years between menopause and menarche, the mortality rate ratio in women with more than 38 reproductive years was 0.5. We also found an inverse relation with age at first birth.

Conclusions—This study supports the hypothesis that an early menarche and a long reproductive period protect against hip fracture mortality. High age at first birth may also be protective.

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Methods

During 1956–59, information about reproductive factors was collected in personal interviews of women who participated in a screening programme for breast cancer in the three Norwegian counties of Vestfold, Nord-Trøndelag, and Aust-Agder. A total of 63 090 women alive and aged 32–74 years at 1 January 1961 were included in this study. The information included age at menarche and menopause (if the woman was postmenopausal), number of fullterm pregnancies, age at first and last birth, duration of lactation, and the number of abortions as well as information about surgery on genital organs (for example, ovariectomy). In particular, the women were asked about the age when the menstruation started and stopped. This was recorded as age at menarche and menopause. For each delivery, the woman was asked to indicate how many months the child had been breast fed. The screening procedures are detailed elsewhere.

Follow up started on 1 January 1961, when the unique personal registration number was introduced in Norway. During follow up from 1961 to 1989, 27 993 of the women included in the cohort died. Information on vital status and cause of death was obtained from files kept at the Central Bureau of Statistics (Statistics Norway), Oslo. A total of 465 women died of a hip fracture—that is, hip fracture was stated on the death certificate. Because of the routines of the Central Bureau of Statistics, it is not possible to say whether the fracture was the underlying cause of death or an associated cause. A fall was, however, reported in all but three of the cases. Thus, the hip fracture must have been important in the process leading to death in the great majority of the cases. No differentiation was made between cervical and trochanteric fractures.

Information on height and weight was available for 50 101 of the 63 090 women, derived from separate measurements made during the time period 1963–1975 as part of compulsory
mass examination for tuberculosis. Body mass index was defined as weight/height\(^2\).

Relations between reproductive variables and hip fracture mortality were investigated by Poisson regression\(^20\) taking into account the number of person years at risk contributed by each woman in different age groups. Women who died of other causes than hip fractures were censored, as were all women alive at the end of follow up, 31 December 1989. Each analysis included all women with known values for the variables considered, and thus the total number of women differed somewhat between analyses. Maximum likelihood estimates of mortality rate ratios with 95% confidence intervals were calculated in a multiplicative model. Likelihood ratio tests for linear trend and departure from a linear trend were performed. The data file with aggregate information on the number of deaths because of hip fracture and person years was generated by the DATAB module in the EPICURE program package.\(^21\) The analyses were carried out by means of the AMFIT module.

As the effect of reproductive variables on hip fracture mortality may be influenced by the age of the women, we performed separate analyses in two age groups 50–79 years and 80 years and above. With a cut off point of 79 the mortality cases remained in the first group to permit reliable statistical analyses. All analyses were adjusted for attained age (five years groups), county of residence and, as an indicator of social class, occupational group (own or husband’s occupation).

**Results**

Table 1 gives the associations between demographic variables and hip fracture mortality in this cohort. The youngest and oldest women who died after a hip fracture were 50 and 99 years old at death, respectively. As expected, a very strong positive relation was seen with age. Women who lived in rural areas at the time of screening had lower risk than women in urban areas. A relatively high hip fracture mortality was observed in the county of Vestfold and a low mortality in Aust-Agder, both counties in the southern part of Norway. This difference remained after adjustment for urban/rural place of residence (data not shown). Women with own or husband’s occupation within industrial work had a relatively high hip fracture mortality, whereas women in the occupational group “farm and forestry work” had a relatively low hip fracture mortality. Thus, we have adjusted for age, county, and occupational group in our analyses.

Table 2 shows the relations between age at menarche and menopause, the number of years between age at menarche and menopause (reproductive period) and hip fracture mortality. In the 50–79 year age group, a statistically significant inverse relation was seen between the number of reproductive years and hip fracture mortality. Compared with women with less than 30 years between menopause and menarche, women with more than 38 reproductive years had a relatively low hip fracture mortality. Compared with women with high age at first birth. A long duration of lactation was not statistically significantly associated with hip fracture mortality. In the 50–79 year age group, a statistically significant positive relation was seen and age at menopause and hip fracture mortality. In the older age group, no relation with hip fracture mortality was observed.

In view of the grouping of values of age at menopause and reproductive period, it is important to carry out an accurate adjustment for current age. To confirm that the relations in women aged 50–79 years were not caused by confounding by age, separate analyses were carried out with adjustment for age in one year instead of five year intervals. This did not, however, influence the relative risk estimates (results not shown).

Relations between reproductive period and hip fracture mortality could have been biased by women with a surgical menopause, who may have a relatively short reproductive period. Thus, separate analyses were also carried out excluding 4131 women who indicated at screening that they had had operations on the ovaries, hysterectomy, unspecified operation of the womb or radiography or radium treatment of the genital organs. This did not, however, weaken the relation between reproductive period and hip fracture mortality (p value for trend = 0.008 in women aged 50–79 years).

Table 3 shows the relations between variables connected to childbearing and hip fracture mortality. No associations were found between parity and hip fracture mortality, but a lower hip fracture mortality was indicated in women with high age at first birth. A long duration of lactation was not statistically significantly associated with hip fracture mortality. No relation was found between the number of abortions reported and hip fracture mortality.

### Table 1: Hip fracture mortality and demographic variables; distribution of person years and mortality rate ratio (MRR) with 95% confidence intervals

<table>
<thead>
<tr>
<th>Birth cohort†</th>
<th>Person years (x1000)</th>
<th>Deaths</th>
<th>MRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1885–1889</td>
<td>218.8 79</td>
<td>0.97</td>
<td>(0.71, 1.34)</td>
</tr>
<tr>
<td>1890–1899</td>
<td>152.1 63</td>
<td>1.37</td>
<td>(0.98, 1.92)</td>
</tr>
<tr>
<td>1885–1889</td>
<td>275.5 93</td>
<td>0.74</td>
<td>(0.54, 1.01)</td>
</tr>
<tr>
<td>1885–1889</td>
<td>108.8 36</td>
<td>0.95</td>
<td>(0.64, 1.42)</td>
</tr>
<tr>
<td>1885–1889</td>
<td>24.9 123</td>
<td>81.06</td>
<td>(59.83, 109.8)</td>
</tr>
<tr>
<td>1885–1889</td>
<td>6.6 57</td>
<td>142.1</td>
<td>(99.28, 203.3)</td>
</tr>
</tbody>
</table>

*Adjusted for attained age in one year intervals. †Adjusted for attained age in five year intervals. ‡Own or husband’s occupation. Adjusted for attained age in five year intervals.
In the subgroup of women with information about height and weight, a highly significant inverse relation (p < 0.001) was found between body mass index and hip fracture mortality. The mortality of hip fracture for obese women (body mass index > 30 kg/m²) was 33% of that for lean women (body mass index < 20 kg/m²). This association was also seen in the 50–79 years age group (p value for linear trend=0.008). The major difference in mortality risk (approximately 60%) seemed to be between that of lean women compared with women with body mass index ≥20 kg/m².

The negative relation between number of reproductive years and hip fracture in women aged 50–79 years was upheld after adjustment for body mass index (p value for linear trend=0.02). Similarly, the negative relation between age at first birth and hip fracture mortality was somewhat strengthened (p value for linear trend=0.05 in both age groups). The mortality rate ratio (MRR) for women with age at first birth ≧35 years was 0.46 (95% confidence intervals 0.26, 0.83) compared with women with age at first birth ≦24 years; nearly identical MRRs were found in both age groups.

After adjustment for body mass index, the negative association between duration of lactation and hip fracture mortality was slightly stronger than that displayed in table 3 for women aged 50–79 years (MRR=0.41, 95% confidence intervals 0.16, 1.10, when

### Table 2: Hip fracture mortality and age at menarche, age at menopause and reproductive period; distribution of person years and mortality rate ratio (MRR) with 95% confidence intervals, by age group

<table>
<thead>
<tr>
<th>Age at menarche*</th>
<th>Person years (×1000)</th>
<th>Total Person years (×1000)</th>
<th>Deaths</th>
<th>MRR (95% CI)</th>
<th>Age at menopause†</th>
<th>Person years (×1000)</th>
<th>Total Person years (×1000)</th>
<th>Deaths</th>
<th>MRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤13</td>
<td>345.0</td>
<td>90</td>
<td>1.00</td>
<td>29</td>
<td>1.00</td>
<td>61</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>393.1</td>
<td>137</td>
<td>1.06</td>
<td>46</td>
<td>1.25 (0.79, 1.99)</td>
<td>91</td>
<td>0.96 (0.69, 1.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>274.9</td>
<td>121</td>
<td>1.14</td>
<td>46</td>
<td>1.62 (1.01, 2.57)</td>
<td>75</td>
<td>0.93 (0.66, 1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>126.4</td>
<td>57</td>
<td>1.04</td>
<td>23</td>
<td>1.61 (0.93, 2.78)</td>
<td>34</td>
<td>0.81 (0.53, 1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥17</td>
<td>74.3</td>
<td>44</td>
<td>1.12</td>
<td>18</td>
<td>2.02 (1.21, 3.64)</td>
<td>26</td>
<td>0.80 (0.51, 1.27)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Hip fracture mortality and parity, age at first and last birth, lactation and abortions; distribution of person years and mortality rate ratio (MRR) with 95% confidence intervals, by age group

<table>
<thead>
<tr>
<th>Parity*</th>
<th>Person years (×1000)</th>
<th>Total Person years (×1000)</th>
<th>Deaths</th>
<th>MRR (95% CI)</th>
<th>Age at first birth (y)†</th>
<th>Person years (×1000)</th>
<th>Total Person years (×1000)</th>
<th>Deaths</th>
<th>MRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>226.8</td>
<td>111</td>
<td>1.00</td>
<td>37</td>
<td>1.00</td>
<td>74</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>529.4</td>
<td>156</td>
<td>0.88</td>
<td>56</td>
<td>0.81 (0.53, 1.24)</td>
<td>100</td>
<td>0.93 (0.69, 1.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>344.9</td>
<td>116</td>
<td>0.88</td>
<td>45</td>
<td>0.97 (0.62, 1.51)</td>
<td>71</td>
<td>0.84 (0.60, 1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>120.5</td>
<td>73</td>
<td>1.02</td>
<td>24</td>
<td>1.22 (0.72, 2.07)</td>
<td>49</td>
<td>0.95 (0.65, 1.37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Abortion‡ | Person years (×1000) | Total Person years (×1000) | Deaths | MRR (95% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>935.9</td>
<td>349</td>
<td>1.00</td>
<td>128</td>
</tr>
<tr>
<td>1</td>
<td>175.1</td>
<td>58</td>
<td>0.98</td>
<td>21</td>
</tr>
</tbody>
</table>

*Among women with known parity, adjusted for attained age, county, and occupational group. †Among parous women with known parity and age at first birth, adjusted for attained age, county, occupational group, and parity. ‡Among parous women with known parity and total lactation, adjusted for attained age, county, occupational group, and parity. §Among women with known parity and number of abortions, adjusted for attained age, county, occupational group, and parity.
Comparing women with \( \geq 30 \) months with women who reported no lactation, \( p \) value for linear trend=0.10. No interaction with parity was indicated in the relation between lactation and hip fracture mortality (results not shown).

**Discussion**

In this 29 year follow up of more than 60 000 women, we found a protective effect of an early menarche, a long reproductive period, and a high age at first birth on the risk of hip fracture mortality.

There is no reason to believe that any of the women included as cases have not sustained a hip fracture. However, some women who die after a hip fracture may not have this diagnosis stated on the death certificate. Meyer and coworkers\(^\text{22} \) have reported a comparison between the incidence and mortality of hip fractures in Norway in 1979. The number of persons who had a diagnosis of hip fracture on their death certificate was about one tenth of the total number of fractures (603 and 5920 subjects, respectively), which is below the expected 12–20% one year excess mortality after a hip fracture.\(^1 \) Still, the strength of the relations between reproductive factors and hip fracture mortality should be affected only if the reproductive history influences the probability that the fracture is included as a cause on the death certificate.

Parity or age at menarche or menopause are unlikely to influence the decision whether the hip fracture should be reported, as this information is not normally available to the physician completing the death certificate. However, if there is a relation between these variables and the total number of diagnoses reported on the death certificate, this may influence the likelihood that the hip fracture is included. A person with many serious or concomitant diseases might have lower probability that the hip fracture is reported. To explain the inverse relation between the number of reproductive years and hip fracture mortality in this way, substantially fewer diagnoses have to be reported in women with a long reproductive period than in women with a short period. This was not the case. In death certificates from women aged 50–79 years with <30 years between menarche and menopause, the mean number of diagnoses was 1.80 compared with 1.74 in women with a long reproductive period (>38 years) (unpublished observations).

Most women who sustain a hip fracture survive.\(^1 \) Thus, during the 29 years of follow up, many hip fractures must have occurred in the cohort that were not included as cases in our study. This may influence the extent to which our results are valid for reproductive factors regarded as risk factors for hip fracture incidence. Possible associations between reproductive factors and hip fracture fatality cannot be excluded, although we are not aware of published results indicating associations between, for example, the number of reproductive years and hip fracture survival.

Our data do not, however, indicate that there is an inverse association between length of reproductive period and total mortality. Such a relation would suggest that this variable is related to general health and thereby to survival, which could explain our result. In women aged 50–79 years, no association was observed between length of reproductive period and total mortality (MRR comparing >38 years with <30 years was 1.07 (95% CI: 0.98, 1.16, \( p \) value for linear trend=0.4). For age at menarche, a weak inverse relation was found (\( p \) value for trend=0.05) (unpublished observations), in contrast with what might be expected if the positive associations between age at menarche and hip fracture mortality should be explained by effects of age at menarche on general health.

The data collected at the screening on parity and age at first and last delivery must be regarded as highly reliable. Information concerning abortions and age at menarche and menopause is more subject to random error, which may weaken possible relations.

The analyses involving age at menopause and length of the reproductive period did not include women who were pre-menopausal at time of screening. Thus, in the younger age groups, women with an early menopause are over-represented in the data set analysed. This does not, however, introduce any bias in the evaluation of associations based on regression analyses, with age at menopause or length of the reproductive period as independent variables. This is because the regression model for prospective studies describes death rates conditional on the particular values of the exposure variables. The actual distribution of exposure values is irrelevant in this connection.

For some exposure variables, such as parity and age at first and last birth, a minor bias is introduced by the reliance on possibly incomplete information collected at screening 2–5 years before the start of follow up. Some women may have given birth to children after the screening took place. In general, this will lead to observed relations that are slightly weaker than the true associations. This bias can therefore not explain the inverse relation found between age at first birth and hip fracture mortality.

Oestrogen, both endogenous\(^{23} \) and exogenous,\(^{7, 5, 21} \) protects against osteoporosis. Our main results are consistent with the concept that a relatively long exposure to

**Key Points**

- Out of a total of 60 000 women followed up for 29 years, 465 women died after a hip fracture.
- In women aged 79 and less, late menarche and a short reproductive period increase hip fracture mortality.
- The most likely explanation to this finding is that long duration of endogenous oestrogens reduces osteoporosis.
- High age at first birth (particularly >34 years) reduces hip fracture mortality.
- Reproductive factors are important for hip fracture mortality.
endogenous oestrogen reduces the hip fracture mortality through the well established positive relation between oestrogen and bone mass.\textsuperscript{23} \textsuperscript{24} The positive relation with age at menarche and inverse relations with age at menopause and the number of reproductive years all point in this direction. An effect of reproductive variables on the risk of falling, the other main risk factor for a hip fracture, may remain speculative, although it has been shown that exogenous oestrogen may improve postural balance in elderly women.\textsuperscript{25} We found an inverse relation between the length of reproductive period and hip fracture mortality. Our results thus support the findings of the MEDOS Study with 2086 cases,\textsuperscript{13} and are consistent with the positive correlation found between number of reproductive years and bone density of the hip as well as the wrist, radius, and spine.\textsuperscript{26}

The number of reproductive years is calculated as the difference between age at menopause and age at menarche. It is noteworthy that, at least in the group of women aged 50–79 years, a stronger effect is found for age at menarche than for age at menopause (MMR=1.15 v 1.05 per year). Although we would not interpret this too far, it may indicate that hormonal factors associated with the teen years may be of greater importance than those associated with the menopause. Possibly, bone mineralisation may be stimulated earlier in women with early menarche, thereby obtaining a higher peak bone mass.\textsuperscript{27} Recently, it has been reported that in postmenopausal women, age at menarche is positively and age at menopause inversely associated with low bone mineral density.\textsuperscript{28}

A reduced impact of the length of the reproductive period was observed with advancing age. This is consistent with findings of Gärdssell and coworkers,\textsuperscript{29} and may simply reflect the longer time since exposure to high levels of endogenous oestrogen. Our finding agrees with the observation that the female excess morbidity of osteoporotic fractures levels off at about 75 years of age, indicating that the duration of the menopause effect is approximately 25 years.\textsuperscript{30} Furthermore, with increasing incidence of a disease (a hip fracture), the relative importance of each risk factor can be attenuated. In old women the bone mass is generally low, and other variables (for example, the tendency to fall) may become more important as predictors for sustaining a hip fracture. Our results suggest a relatively strong inverse relation between age at first birth and hip fracture mortality, a relation found to be upheld after adjustments for body mass index. This association was independent of age group (50–79 or >80 years). It has previously been reported that a first pregnancy before age 20 is associated with lower bone mass density,\textsuperscript{31} but case-control studies have shown no relation, or a positive relation, between age at first birth and hip fracture risk.\textsuperscript{28} The lack of any relation between parity and hip fracture mortality is consistent with combined results from several previous studies.\textsuperscript{7} \textsuperscript{10} \textsuperscript{12}–\textsuperscript{17} The possible effects of multipar-
approximately 82%. This is the relevant age group as only postmenopausal women contributed to the analysis of reproductive period as risk factor for hip fracture.

Confounding by alcohol drinking is even less likely because in 1973 less than 2% of the Norwegian women aged 18 and more had a daily consumption of alcoholic beverages corresponding to more than 20 ml pure alcohol. Alcohol consumption and smoking prevalence among women included in this study living predominantly in rural parts of the country were probably even lower. Thus, confounding by alcohol drinking or cigarette smoking is not likely to be of major importance for our results.

Coffee drinking is a common habit in Norway. A weak positive relation between coffee consumption and parity has been found in middle aged women in Norway. However, there must be a rather strong association between coffee consumption and reproductive variables to influence our findings notably.

In summary, in this large cohort of Norwegian women, we found a statistically significant protective effect of an early menarche and a long reproductive period on the mortality of hip fractures in women aged less than 80. There was also evidence for a protective effect of high age at first birth. However, in view of the sampling errors associated with our estimates, these relations should be studied further in other prospective studies with hip fracture incidence as the end point.

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