Hormone Replacement Therapy and Hip Fracture Risk: Effect Modification by Tobacco Smoking, Alcohol Intake, Physical Activity, and Body Mass Index

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The authors prospectively studied the overall effect of hormone replacement therapy (HRT) on hip fracture risk and the effect modification by behavioral habits and body mass index. A total of 6,159 postmenopausal women from the Copenhagen Center for Prospective Population Studies, Copenhagen, Denmark, with initial examination in 1976–1978 were followed until 1993. During follow-up 363 hip fractures were identified. Women who reported current use of HRT had a lower risk of hip fracture as compared with women who were nonusers (relative risk (RR) = 0.71; 95 percent confidence interval (CI): 0.50, 1.01). Use of HRT was associated with a lower risk of hip fracture in former (RR = 0.55; 95 percent CI: 0.22, 1.37) and current (RR = 0.61; 95 percent CI: 0.38, 0.99) smokers but not in never smokers (RR = 1.10; 95 percent CI: 0.60, 2.03). HRT was also associated with lower risk of hip fracture among alcohol drinkers (RR = 0.36; 95 percent CI: 0.14, 0.90) and among sedentary women (RR = 0.42; 95 percent CI: 0.18, 0.96) but not among nondrinkers (RR = 0.99; 95 percent CI: 0.61, 1.61) and physically active women (RR = 0.92; 95 percent CI: 0.42, 2.04). There was no evidence of interaction between use of HRT and body mass index. In conclusion, the protective effect of HRT on hip fracture appears to be strongest in women who ever smoked, in women who drink alcohol, and in women who are sedentary. The results suggest that history of behavioral habits offers important information concerning the probable degree of protection against hip fracture afforded by HRT. Am J Epidemiol 1999; 150:1085–93.

Evidence has accumulated that hormone replacement therapy (HRT), initiated soon after spontaneous menopause or oophorectomy, prevents bone loss and decreases the risk of postmenopausal fractures (1–7). The protective effect of HRT seems to increase by duration of use but tends to diminish rapidly after discontinuation, suggesting that for protection against fracture, HRT should be continued indefinitely after menopause (6–11). In order to counterbalance potential adverse effects of long-term HRT, including increased risk for breast cancer, venous thromboembolism, and pulmonary embolism (12–14), strategies to identify the subset of women who achieve the largest degree of protection against fracture from the treatment must be determined. A physician’s decision to recommend fracture-protective HRT to a healthy postmenopausal woman is usually guided by her family history of osteoporosis together with her status of behavioral and physiologic characteristics that have been shown to influence the risk of osteoporotic fractures. These factors include tobacco smoking, alcohol use, physical activity, body weight, calcium intake, parity, and age at menopause (8, 15–17). Our actual knowledge of the potential effect modifications of behavioral and physiologic factors on the efficacy of HRT on fractures, however, is sparse, and data concerning the effect modification by smoking are conflicting (6, 9, 18, 19).

The purpose of the present study was to evaluate the overall effect of HRT on hip fracture risk and to examine whether tobacco smoking, alcohol intake, physical activity, and body mass index modify this effect.
MATERIALS AND METHODS

Study population

The Copenhagen Center for Prospective Population Studies compiles data from three Danish prospective population studies: The Copenhagen City Heart Study (CCHS), the Copenhagen County Center of Preventive Medicine study, and the Copenhagen Male Study. Information on HRT was available in the CCHS and the Copenhagen County Center of Preventive Medicine study. However, because of different phrasing of the questions concerning use of HRT in the two studies (current use of HRT yes/no and ever use of HRT yes/no, respectively), data from the studies could not be collapsed. As the CCHS contributed data on 363 of the 419 incident hip fractures among postmenopausal women during follow-up and on more than 80 percent of the total postmenopausal person-time, this population study was selected for the present study. The CCHS has been described in detail previously (20). Briefly, the CCHS comprises randomly selected, age-stratified men and women aged 20–93 years from a defined area of central Copenhagen. The baseline examination took place in 1976–1978 and included a total of 14,223 subjects (response rate = 74 percent) of whom 7,712 were females. The present study is based on the 6,188 women who were postmenopausal at the baseline examination. As the outcome in the present study concerned the occurrence of first-ever hip fractures, women with an identified hip fracture before entrance into the study were excluded (n = 29), leaving 6,159 postmenopausal women to be included in the analyses.

Examination procedure

The examination included a self-administered questionnaire with detailed questions regarding behavioral habits and other health-related items.

Ascertainment of menopause

All women were asked whether their menstruation had stopped (yes or no) and at what age this happened. Information on previous hysterectomy was not available.

Ascertainment of hormone replacement therapy

The postmenopausal women were asked whether they currently received hormone replacement therapy (yes or no). Information on the duration of HRT was not available. In the present study, hormone replacement therapy includes all types of systemically administered hormones for postmenopausal replacement therapy, that is, continuous unopposed estrogens, sequential/cyclic estrogen-progestogen regimens, and continuous combined estrogen-progestogen regimens.

Other covariates

Age at menopause. For the analysis, three menopausal age groups were defined: 1) less than 45 years, 2) 45–52 years, and 3) more than 52 years.

Parity. Women were classified as 1) nulliparous or as having had 2) one or two births, 3) three births, and 4) four or more births.

Alcohol intake. All women were asked about the average number of drinks consumed per week. One drink contains on average 12 g of alcohol. The subjects were classified according to their total weekly alcohol intake: 1) less than one drink per week, 2) from one to six drinks per week, 3) 7 drinks per week or more.

Smoking habits. The women reported if they were never smokers, exsmokers, or current smokers. Current smokers were classified according to the amount of tobacco smoked per day. For the analysis, five groups were defined: 1) never smokers, 2) exsmokers, 3) smokers of 1–14 g per day, 4) smokers of 15–24 g per day, and 5) smokers of 25 g or more per day. One cigarette contains on average 1 g of tobacco.

Physical activity at leisure time. The women reported whether they were 1) sedentary, 2) moderately physically active 2–4 hours per week, 3) moderately physically active more than 4 hours per week or energetically physically active 2–4 hours per week, or 4) energetically physically active more than 4 hours per week or participated in sports competition. Because of very few subjects in the last category, activity levels 3 and 4 were grouped together in the analyses.

Educational level. The subjects further reported if they had attended school: 1) less than 8 years, 2) between 8 and 11 years, or 3) 12 years or more.

Cohabitation. The subjects reported whether they lived alone or not.

Marital status. The subjects reported if they were 1) married, 2) unmarried, 3) divorced, or 4) widowed.

Body mass index. Weight in light clothes and height without shoes were measured and, from these, body mass index was calculated as weight (kg)/height (m)\(^2\). For the analysis, three body mass index groups were defined: 1) less than 20 kg/m\(^2\), 2) from 20 to less than 25 kg/m\(^2\), and 3) 25 kg/m\(^2\) or more.

The exposure status at the baseline examination was used to define the individual exposure status throughout the time of follow-up.

Follow-up

The time of observation was calculated from the date of entry into the study to the date of the first-ever
hip fracture, death, disappearance, emigration, or end of follow-up (December 31, 1993), whichever came first. Less than a half percent of the study subjects were lost to follow-up because of disappearance or emigration.

Information on hip fractures suffered by the study subjects during follow-up was obtained through individual-based linkage to the National Register of Hospital Discharges by means of the personal identification number. The Danish National Register of Hospital Discharges contains data on all hospital discharges in Denmark since 1977 and therefore provides complete coverage of the cases in the present study (21, 22). The register includes patient and hospital unit specified discharge diagnoses according to the International Classification of Diseases, Injuries, and Causes of Death, Eighth Revision (ICD-8) (22). Vital status of the population sample was followed by using the unique personal identification number in the Danish National Central Person Register. The follow-up in the present study concerned the first occurrence of a cervical or trochanteric hip fracture (ICD-8 codes 820.00–820.09). Subjects with ICD-8 codes 820 modified as “sequelae” (resulting condition after previous hip fracture), “observatio pro” (suspected but not verified hip fracture), “recidivans” (recurrent hip fracture), or “antea” (previous hip fracture) were excluded.

Validation of hip fracture cases

In order to test the accuracy of hip fracture diagnoses from the National Register of Hospital Discharges, we identified a sample of 110 unmodified, first-time registered, ICD-8 codes 820 among men and women in the Copenhagen Center for Prospective Population Studies for validation by review of hospital records. A total of 102 hip fracture codes correctly represented first-ever hip fractures caused by low energy traumas, that is, a fall at the same level. Four hip fracture cases were caused by high energy trauma or malignancy; another four fractures represented a second hip fracture with an unregistered first hip fracture from the period not covered by the National Register of Disease. Thus, approximately 93 percent of all unmodified, first-time registered codes 820 in the National Register of Disease are likely to represent low energy, first-ever fractures.

Statistical analysis

The data were analyzed by means of multiplicative Poisson regression models using the STATA 5.0 statistical package (23). The models were estimated by the maximum likelihood method, and the effects of covariates were tested by likelihood ratio tests.

RESULTS

During 183,409 postmenopausal person-years, 363 first hip fractures were identified. Hip fracture incidence doubled every 5 years after age 60, and the mean age at hip fracture was 74 years. The prevalence of HRT and baseline characteristics of the postmenopausal women by hormone use are given in table 1.

Women who at baseline reported current use of HRT had a lower risk of hip fracture when compared with current nonusers after adjustment for confounding factors (relative risk (RR) = 0.71; 95 percent confidence interval (CI): 0.50, 1.01). In general, adjustment for potential confounders did not alter the age-adjusted estimates substantially (table 2).

In the present study population, hip fracture was significantly associated with tobacco smoking, physical
TABLE 1. Baseline characteristics by use of hormone replacement therapy among postmenopausal women in the Copenhagen City Heart Study, Copenhagen, Denmark, 1977–1993

<table>
<thead>
<tr>
<th>Hormone replacement therapy</th>
<th>No.</th>
<th>%</th>
<th>Sedentary at leisure time (%)</th>
<th>Alcohol Intake &gt;7 drinks/week (%)</th>
<th>Current smokers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current users</td>
<td>1,314</td>
<td>21.3</td>
<td>21.0</td>
<td>25.0</td>
<td>62.9</td>
</tr>
<tr>
<td>Current nonusers</td>
<td>4,832</td>
<td>78.7</td>
<td>21.5</td>
<td>20.8</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean age at baseline (years)</th>
<th>Mean age at menopause (years)</th>
<th>Nulliparous (%)</th>
<th>Mean body mass index (kg/m²)</th>
<th>&lt;8 years of school education (%)</th>
<th>Live alone (%)</th>
<th>Married (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current users</td>
<td>55.4 (5.8)*</td>
<td>46.7 (5.4)</td>
<td>22.0</td>
<td>24.4 (4.2)</td>
<td>47.7</td>
<td>31.5</td>
<td>61.4</td>
</tr>
<tr>
<td>Current nonusers</td>
<td>59.5 (8.0)</td>
<td>47.4 (5.4)</td>
<td>25.2</td>
<td>25.3 (4.6)</td>
<td>55.5</td>
<td>41.0</td>
<td>52.9</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, standard deviation.

TABLE 2. Age- and multivariate-adjusted relative risk of hip fracture according to baseline use of hormone replacement therapy among postmenopausal women in the Copenhagen City Heart Study, Copenhagen, Denmark, 1977–1993

<table>
<thead>
<tr>
<th></th>
<th>Hip fractures (no.)</th>
<th>Person-years</th>
<th>Age-adjusted relative risk</th>
<th>Multivariate-adjusted relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hormone replacement therapy</td>
<td>326</td>
<td>64,438</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current hormone replacement therapy</td>
<td>37</td>
<td>18,828</td>
<td>0.71 (0.50, 1.00)†</td>
<td>0.71 (0.50, 1.01)†</td>
</tr>
</tbody>
</table>

* Adjusted for age, body mass index, physical activity, smoking, alcohol intake, cohabitation, marital status, school education, age at menopause, and parity.
† Numbers in parentheses, 95% confidence interval.

inactivity, and low body mass index while no significant association between alcohol intake and hip fracture was observed (table 3). In order to test whether these factors modified the fracture-preventive effect of HRT, we performed stratified analyses. As given in table 4, the apparent protective effect of HRT was restricted to current smokers (RR = 0.61; 95 percent CI: 0.38, 0.99) and exsmokers (RR = 0.55; 95 percent CI: 0.22, 1.37), while never smokers experienced no such effect (RR = 1.10; 95 percent CI: 0.60, 2.03). Statistical testing for the presence of an interaction between HRT and smoking supported this finding. Introduction of a first-order interaction term between “ever/never smoking” and “current use of HRT (yes/no)” in the regression model significantly improved the fit of the model to the data (p value of log likelihood ratio test = 0.05). Moreover, the protective effect of HRT gradually increased with the amount of tobacco smoked per day from a relative risk of 0.74 (95 percent CI: 0.40, 1.35) in light smokers to 0.50 (95 percent CI: 0.21, 1.16) in smokers of 15–24 g of tobacco per day to 0.35 (95 percent CI: 0.04, 2.71) in women who smoked 25 g or more of tobacco per day (table 4).

Alcohol drinkers also seemed to experience a protective effect of HRT on hip fracture. The stratified analysis showed a gradually increasing protective effect with increasing alcohol intake, from a relative risk of 0.67 (95 percent CI: 0.36, 1.22) in women who drank 1–6 drinks per week to a relative risk of 0.36 (95 percent CI: 0.14, 0.90) in women who drank seven or more drinks per week, while no such effect was observed in abstainers (RR = 0.99; 95 percent CI: 0.61, 1.61) (table 4). A model including the interaction terms between alcohol intake and HRT, however, did not improve the fit of the model to data (p value of log likelihood ratio test = 0.08), indicating that the stratified estimates did not differ significantly.

The apparent protective effect of HRT on hip fracture also seemed to be influenced by the level of physical activity at leisure time. Stratified analysis revealed that sedentary women experienced a high degree of fracture protection by HRT (RR = 0.42; 95 percent CI: 0.18, 0.98), while the effect leveled off with increasing physical activity and nearly reached 1.0 in women who were moderately active for at least 4 hours per week (table 4). The interaction between physical activity and HRT, however, was not significant at the 5 percent level (p value of log likelihood ratio test = 0.22).
TABLE 3. Age- and multivariate-adjusted relative risk of hip fracture according to behavioral habits and body mass index among postmenopausal women in the Copenhagen City Heart Study, Copenhagen, Denmark, 1977–1993

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Hip fractures (no.)</th>
<th>Person-years</th>
<th>Age-adjusted relative risk</th>
<th>Multivariate-adjusted relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>112</td>
<td>23,446</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Exsmokers</td>
<td>65</td>
<td>12,914</td>
<td>1.28 (0.94, 1.73)†</td>
<td>1.34 (0.98, 1.83)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>185</td>
<td>46,889</td>
<td>1.48 (1.18, 1.86)</td>
<td>1.31 (1.02, 1.68)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>172</td>
<td>32,657</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–6 drinks/week</td>
<td>115</td>
<td>32,355</td>
<td>0.85 (0.67, 1.07)</td>
<td>0.85 (0.67, 1.10)</td>
</tr>
<tr>
<td>7 drinks/week or more</td>
<td>75</td>
<td>18,289</td>
<td>0.96 (0.73, 1.25)</td>
<td>0.90 (0.68, 1.20)</td>
</tr>
<tr>
<td>Leisure-time physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>106</td>
<td>16,413</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate activity 2–4 hours/week</td>
<td>187</td>
<td>46,649</td>
<td>0.68 (0.53, 0.86)</td>
<td>0.71 (0.55, 0.91)</td>
</tr>
<tr>
<td>Moderate activity &gt;4 hours/week</td>
<td>70</td>
<td>18,318</td>
<td>0.67 (0.50, 0.91)</td>
<td>0.65 (0.48, 0.89)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 kg/m²</td>
<td>49</td>
<td>7,055</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>20–25 kg/m²</td>
<td>174</td>
<td>40,141</td>
<td>0.50 (0.37, 0.69)</td>
<td>0.57 (0.41, 0.79)</td>
</tr>
<tr>
<td>≥25 kg/m²</td>
<td>140</td>
<td>36,024</td>
<td>0.37 (0.26, 0.51)</td>
<td>0.36 (0.27, 0.54)</td>
</tr>
</tbody>
</table>

* From Poisson regression models with the variables in the table and age, hormone replacement therapy, age at menopause, parity, cohabitation, marital status, and school education as covariates.
† Numbers in parentheses, 95% confidence interval.

As given in table 4, body mass index did not modify the effect of HRT (p value of log likelihood ratio test = 0.94).

DISCUSSION

We find that use of HRT is associated with a 30 percent decrease in risk of hip fracture. Smoking habits significantly modify the apparent protective effect of HRT on hip fracture. Thus, only women who ever smoked seem to achieve a protective effect from the treatment, while never smokers experience no such effect. Alcohol intake and physical activity do not significantly modify the effect of HRT on hip fracture. However, we find a clear tendency toward a more pronounced protective effect of the treatment in women who drink alcohol and in sedentary women as compared with abstainers and nonsedentary women, respectively. Body mass index does not appear to influence the effectiveness of HRT, suggesting that HRT protects lean women and obese women against hip fracture equally well.

Our findings support previous observational studies that HRT is associated with lower risk of hip fracture (4, 6, 7, 11, 18, 24–29). The magnitude of the protective effect is consistent with the finding of a 25 percent reduction in hip fracture risk in women who ever used hormones in a recent meta-analysis (30).

We found that HRT apparently was effective in decreasing the risk of hip fracture in smokers. This observation conflicts with previous findings that smoking negates the positive effect of HRT on postmenopausal bone loss and osteoporotic fractures (19, 31). Jensen et al. (31) observed that hormone-treated smokers had lower levels of serum estrogens and a lower treatment response on bone mineral content as compared with hormone-treated nonsmokers. The authors hypothesized that smoking may induce increased hepatic degradation of exogenous estrogen. Results from the Framingham Study supported this hypothesis by showing that the protective effect of HRT on hip fracture was restricted to postmenopausal women who never smoked (19). Our contradictory finding cannot be explained by a high prevalence of percutaneously (extrahepatic) administered HRT in the present study, since this type of administration was not introduced in Denmark until late in the 1980s and still is rather uncommon among Danish women. Furthermore, observations from several other studies contradict the existence of a negative effect of smoking on exogenous estrogen. Williams et al. (18) observed that HRT prevented fractures in smokers, particularly among those who were slim. Likewise, in a cohort of elderly white women, Cauley et al. (6) observed a protective effect of HRT in current smokers. Moreover, if smoking negates the positive effect of HRT, then smoking may be expected to have a similar effect on other disease endpoints. However, studies that used bone mass density, cardiovascular diseases,
### TABLE 4. Baseline hormone replacement therapy (HRT) and risk of hip fracture according to behavioral factors and body mass index among postmenopausal women in the Copenhagen City Heart Study, Copenhagen, Denmark, 1977–1993

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Hip fractures (no.)</th>
<th>Person-years</th>
<th>Age-adjusted relative risk</th>
<th>Multivariate-adjusted relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>99</td>
<td>19,100</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>13</td>
<td>4,304</td>
<td>1.17 (0.66, 2.11)†</td>
<td>1.10 (0.60, 2.03)</td>
</tr>
<tr>
<td>Former smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>60</td>
<td>10,059</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>5</td>
<td>2,841</td>
<td>0.50 (0.20, 1.25)</td>
<td>0.55 (0.22, 1.37)</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>166</td>
<td>35,124</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>19</td>
<td>11,679</td>
<td>0.59 (0.36, 0.96)</td>
<td>0.61 (0.38, 0.99)</td>
</tr>
<tr>
<td>1–14 g/day‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>97</td>
<td>20,048</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>12</td>
<td>6,364</td>
<td>0.71 (0.39, 1.30)</td>
<td>0.74 (0.40, 1.35)</td>
</tr>
<tr>
<td>15–24 g/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>56</td>
<td>12,711</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>6</td>
<td>4,490</td>
<td>0.47 (0.20, 1.09)</td>
<td>0.50 (0.21, 1.16)</td>
</tr>
<tr>
<td>25 g/day or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>13</td>
<td>2,365</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>1</td>
<td>825</td>
<td>0.34 (0.04, 2.62)</td>
<td>0.35 (0.04, 2.71)</td>
</tr>
<tr>
<td>Alcohol intake (drinks/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>168</td>
<td>32,777</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>25</td>
<td>9,141</td>
<td>1.02 (0.64, 1.64)</td>
<td>0.99 (0.61, 1.61)</td>
</tr>
<tr>
<td>1–6 drinks/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>109</td>
<td>28,551</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>16</td>
<td>10,634</td>
<td>0.85 (0.35, 1.18)</td>
<td>0.67 (0.36, 1.22)</td>
</tr>
<tr>
<td>7 drinks/week or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>86</td>
<td>17,210</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>10</td>
<td>7,289</td>
<td>0.36 (0.14, 0.88)</td>
<td>0.36 (0.14, 0.90)</td>
</tr>
<tr>
<td>Physical activity at leisure time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>100</td>
<td>12,657</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>6</td>
<td>3,742</td>
<td>0.41 (0.18, 0.94)</td>
<td>0.42 (0.18, 0.98)</td>
</tr>
<tr>
<td>Moderate activity 2–4 hours/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>164</td>
<td>37,215</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>23</td>
<td>11,327</td>
<td>0.78 (0.50, 1.20)</td>
<td>0.79 (0.50, 1.23)</td>
</tr>
<tr>
<td>Moderate activity &gt;4 hours/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>62</td>
<td>14,535</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>8</td>
<td>3,758</td>
<td>1.02 (0.49, 2.15)</td>
<td>0.92 (0.42, 2.04)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>197</td>
<td>34,193</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>24</td>
<td>11,299</td>
<td>0.60 (0.24, 1.51)</td>
<td>0.66 (0.26, 1.68)</td>
</tr>
<tr>
<td>20–24 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>107</td>
<td>23,378</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Current HRT</td>
<td>11</td>
<td>6,266</td>
<td>0.71 (0.45, 1.13)</td>
<td>0.74 (0.46, 1.17)</td>
</tr>
<tr>
<td>≥25 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT</td>
<td>22</td>
<td>6,748</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
| Current HRT      | 2                   | 1,200        | 0.72 (0.38, 1.34)           | 0.70 (0.36, 1.33)                     

* Adjusted for age, age at menopause, parity, cohabitation, marital status, and school education and, respectively, body mass index, physical activity, smoking, and alcohol intake.
† Numbers in parentheses, 95% confidence interval.
‡ Amount of tobacco smoked per day in grams.

* Am J Epidemiol Vol. 150, No. 10, 1999
stroke, or all-cause mortality as the outcome measure-
ment have documented a protective effect of HRT
among smokers (1, 32–34). Women who smoke seem
to experience a greater postmenopausal bone loss than
do nonsmokers (35, 36). Deceleration of the extensive
postmenopausal bone loss in smokers by HRT is likely
to account for the observed effectiveness of the ther-
apy on hip fracture risk among smokers. Our finding
of a gradually increased hip fracture protection by
HRT with the amount of tobacco smoked further sug-
gests that the rate of postmenopausal bone loss in
smokers correlates with the amount of tobacco
smoked.

We observed no hip fracture-preventive effect of
HRT in women who never smoked. As compared with
smokers, who physiologically seem to act as though
they are relatively estrogen deficient (37), never smok-
ers are likely to have had optimal endogeneous es-
rogen stimulation of bone during their lifetime. Together
with an undisturbed rate of postmenopausal bone loss,
this may explain why no additional protective effect of
exogenous hormones on hip fracture risk was observed
among never smokers in our study.

Postmenopausal women in our study had a rather
low alcohol intake, and no association between alcohol
intake and hip fracture was observed in this range of
intake. Despite this, the apparent protective effect of
HRT gradually increased by increasing level of alcohol
intake, suggesting that alcohol may potentiate the pro-
tective effect of HRT. This observation is supported by
the recent finding that acute alcohol ingestion leads to
sustained elevation in circulating estradiol levels in
current users of HRT (38). On the other hand, alcohol
intake did not modify the effect of HRT on bone min-
eral density in women from the Postmenopausal
Estrogen/Progestin Intervention Trial (1).

Subjects who are physically active during leisure
time appear to have a lower risk of hip fracture, as
compared with subjects who are sedentary (8, 39, 40).
The protective effect of physical activity on hip frac-
ture is probably mediated through a higher bone mass
cased by mechanical stress on the skeleton or through
improvements in muscular strength. Our observation,
that the apparent protective effect of HRT gradually
leveled off by increasing level of physical activity,
suggests that fracture-preventive HRT may be espe-
cially relevant in women who are sedentary.

Some methodological problems may have influ-
enced the validity of our results. First, our data on HRT
were limited with respect to information on age at
onset of therapy, duration of therapy, and specification
of type of therapy. Second, the information on behav-
ioral habits was self-reported and no validation was
performed. In this context, however, it may be noted
that self-reported alcohol intake has been shown to
predict liver disease in the present cohort (41). Like-
wise, a reliability test of self-reported alcohol intake
conducted in another cohort from the Copenhagen Center of Prospective Studies showed
consistency with the self-reported alcohol intake and
the alcohol consumption achieved by a diet interview
(42). Moreover, the four-point physical activity scale
has been shown to discriminate sedentary and physi-
ically active subjects with respect to maximum oxygen
uptake (43). Finally, the prevalence of smoking in the
study population resembles the prevalence observed
in other Danish population samples at the same time
(44). Still, the presence of incorrect ascertainment of
behavioral habits in our study cannot be ruled out.
However, as the ascertainment of behavioral habits
preceded the occurrence of hip fracture, the potential
misclassification is likely to be randomly distributed
between subjects with and subjects without hip frac-
ture. Likewise, the misclassification of behavioral
habits is likely to occur in similar proportions among
users and nonusers of HRT.

Third, information on HRT and behavioral habits
in the present study was assessed only at baseline. Since
the status of any of these variables may have changed
during the follow-up period, this may be another
source of misclassification in our study. However, as
this misclassification is unlikely to be related to the
outcome of interest (hip fracture), it is most likely an
underestimate of any true association between expo-
sures and hip fracture. For example, women in our
study who initiated HRT after the baseline exami-
nation are misclassified as nonusers, resulting in an
underestimation of the fracture-preventive effect of
HRT. Moreover, assuming that the effect of previous
HRT is lasting, some women classified as current
nonusers may have used HRT previously, resulting in
underestimation of the protective effect of current
HRT. Likewise, changes in behavioral habits during
the course of follow-up may have resulted in underes-
timation of the true association between these habits
and hip fracture just as the misclassification may have
diluted the effect modification of behavioral habits on
the fracture-preventive effect of HRT.

A certain degree of overestimation of the effect of
HRT on hip fracture risk may, however, also be present
in our study. If HRT systematically is preferred by
women who have a lower risk of fracture because of a
generally better health behavior, the protective effect
of HRT may be overestimated ("the healthy user
effect") (45, 46). In the present study, nonusers and
users of HRT differed by several sociodemographic
and biologic characteristics. Adjustment for school
education, marital status, and cohabitation, alone and
together with other potential confounding factors, did not alter the age-adjusted risk estimates substantially. However, other unmeasured factors, such as diet, may potentially have confounded our results. Whether the seemingly protective effect of HRT on hip fracture is determined by the "healthy user effect" will be clarified when results from ongoing randomized trials are analyzed.

In conclusion, use of HRT seems to reduce the risk of hip fracture by approximately 30 percent. Smoking does not negate the apparent protective effect of HRT on hip fracture. The fracture-protective effect of HRT appears to be strongest in women who smoke, who drink alcohol, and who are physically inactive. Our results suggest that a history of behavioral habits offers important information concerning the probable degree of protection against hip fracture afforded by HRT, and they stress the importance of doctors' taking this information into account when considering long-term HRT in the prevention of osteoporotic fractures in women.

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REFERENCES

31. Jensen J, Christiansen C, Rödbro P. Cigarette smoking, serum


