# Fracture Incidence in Relation to the Pattern of Use of Hormone Therapy in Postmenopausal Women

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**Context** Evidence is limited on the effects of different patterns of use of postmenopausal hormone therapy on fracture incidence and particularly on the effects of ceasing use.

**Objective** To investigate the effect of different patterns of hormone therapy use on fracture incidence.

**Design, Setting, and Participants** Prospective study of 138737 postmenopausal women aged 50 to 69 years recruited from the UK general population in 1996-1998 (the Million Women Study) and followed up for 1.9 to 3.9 years (average, 2.8 years) for fracture incidence.

**Main Outcome Measure** Adjusted relative risk (RR) for incident fracture (except fracture of the fingers, toes, and ribs) in hormone therapy users compared with never users at baseline.

**Results** A total of 5197 women (3.7%) reported 1 or more fractures, 79% resulting from falls. Current users of hormone therapy at baseline had a significantly reduced incidence of fracture (RR, 0.62; 95% confidence interval [CI], 0.58-0.66; $P<.001$). This protection was evident soon after hormone therapy began, and the RR decreased with increasing duration of use ($P=.001$). Among current users at baseline the RR of fracture did not vary significantly according to whether estrogen-only, estrogen-progestin, or other types of hormones were used (RR [95% CI], 0.64 [0.58-0.71], 0.58 [0.53-0.64], and 0.67 [0.56-0.80], respectively; $P=.19$), nor did it vary significantly according to estrogen dose or estrogen or progestin constituents. The RR associated with current use of hormone therapy did not vary significantly according to 11 personal characteristics of study participants, including their age at menopause, body mass index, and physical activity. Past users of hormone therapy at baseline experienced no significant protection against fractures (RR, 1.07; 95% CI, 0.99-1.15); incidence rates returned to those of never-users within about a year of ceasing use.

**Conclusions** All types of hormone therapy studied confer substantial protection against fracture while they are used. This protection appears rapidly after use commences and wears off rapidly after use ceases. The older women are, the greater is their absolute reduction in fracture incidence while using hormone therapy.

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POSTMENOPAUSAL WOMEN WHO use hormone therapy are known to have a reduced incidence of fracture compared with women who do not.[1-3] However, there is limited information on how long this protective effect persists after use ceases, how different types of hormones affect the risk of fracture, and how hormone therapy affects the risk of fracture of different bones. This large cohort study of postmenopausal UK women investigates the effect of various patterns of hormone therapy use on the incidence of fracture.

## METHODS

### Data Collection and Definitions

The Million Women Study is a population-based prospective study designed primarily to investigate the health effects of hormone therapy; its methods are described elsewhere.[4] More than 1 million women were recruited between 1996 and 2001 and, beginning in 1999, a follow-up questionnaire has been mailed to study participants 2 to 3 years after initial recruitment. The recruitment questionnaire includes questions on lifestyle and sociodemographic factors, reproductive factors, past health, and use of hormone therapy. The follow-up questionnaire includes questions on any fractures sustained in the last 5 years and, if relevant, the anatomical site of the fracture, the month and year it occurred, and the mechanism of injury (eg, a fall, automobile accident, another accident, fracture found on radiography without the participant know-

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ing it had occurred, or in some other way). Both questionnaires can be viewed at http://www.millionwomenstudy.org. All participants gave written informed consent to take part, and ethical approval for the study was provided by the Oxford and Anglia Multi-Centre Research Ethics Committee.

An incident fracture was defined as any fracture reported at follow-up to have occurred after the date of recruitment into the study but excluding fractures of the fingers (and thumbs), toes, and ribs. Women with previous fracture were not excluded. Current, past, and never use of hormone therapy were defined according to what was reported on the recruitment questionnaire at baseline. Women were asked which specific proprietary preparation of hormone therapy they had used most recently, and the preparations were grouped, as described previously,[5] according to the hormonal constituents of each preparation listed in the British National Formulary.[6] Women whose menstruation had ceased either naturally or as the result of a bilateral oophorectomy were defined as postmenopausal. As described previously,[5] women aged 53 years and older who had had a hysterectomy without oophorectomy were also defined as postmenopausal, as were women aged 53 years and older who had begun use of hormone therapy before their natural menopause. Sensitivity analyses were performed to examine the effect of excluding these women from the analyses.

Women recruited into the Million Women Study between June 1996 and March 1998 were sent a follow-up questionnaire (and one reminder, if necessary) between October 1999 and November 2000. This effectively constituted the first quarter of women recruited into the Million Women Study cohort and included 242 167 postmenopausal women aged 50 to 69 years. By November 2001, 150 706 (62%) had returned a completed questionnaire within 4 years from recruitment. Replies from these women were checked, coded, and analyzed in advance of the remainder of the cohort because follow-up is still not complete for the entire cohort, and power calculations indicated that the numbers of incident fractures in this sample would be sufficient to provide statistically reliable answers to the most important outstanding questions about the effect of different patterns of use of hormone therapy on the incidence of fracture. Response rates did not differ substantially according to age at baseline (60% for 50-54 years, 63% for 55-59 years, 63% for 60-64 years, and 66% for 65-69 years) and use of hormone therapy at baseline (65% for current, 62% for past, and 61% for never users; 65% among current users of estrogen-only, 65% for current estrogen-progestin users, and 63% for current users of other types of hormone therapy). The only factor that appeared to have an appreciable effect on response rates was a woman's socioeconomic status, measured as "deprivation index" on the basis of car and home ownership, overcrowding, and unemployment in the area of residence[7] (68% for women in the highest, 64% for the middle, and 55% for the lowest tertiles of socioeconomic status).

### Analysis

Of the 150 706 postmenopausal women who returned a completed follow-up questionnaire, 4376 (2.9%) who reported a history of cancer (other than nonmelanoma skin cancer) and 5188 (3.4%) who reported a history of osteoporosis at baseline were excluded from the analyses (because the presence of these illnesses could affect both the prescribing of hormone therapy and the subsequent incidence of fracture). Also excluded were 1843 (1.2%) with missing data on use of hormone therapy at baseline and 562 (0.3%) who reported a fracture but did not provide the date it occurred, leaving 138 737 women for the main analyses.

Relative risks (RRs) for fracture were estimated using a Cox regression model, in which the underlying time variable was defined as the time from recruitment to the first fracture or to the return of the follow-up questionnaire, whichever was earliest. For the 336 women who reported more than 1 fracture during the follow-up period (6.5% of all women reporting any fracture), multiple fractures had been sustained simultaneously by about half and for the remainder it was not always possible to determine which of the fractures had occurred first. Hence, in analyses examining fracture risk separately by anatomical site, women reporting multiple fractures were assigned to just 1 relevant site, according to the following hierarchy: hip, spine, shoulder, leg, foot, ankle, and wrist or arm. Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (in 2-year intervals [10 categories]), region of recruitment, socioeconomic status (in tertiles), time since menopause (<5, 5-9, ≥10 years), body mass index (<22.5, 22.5-24.9, ≥25 [measured as weight in kilograms divided by height in meters squared]), and physical activity (strenuous exercise rarely/never, less than once per week, 1 or more times per week). The effect of further adjustment for cigarette smoking, alcohol consumption, parity, previous use of oral contraceptives, and previous illness was examined. Tests of significance were 2-sided with $P<.05$ set as the level of significance. The STATA computing package was used for all analyses.[8]

## RESULTS

The 138 737 postmenopausal women included in the analyses were followed up for 382 637 person-years, an average of 2.8 years per woman (range, 1.9-3.9 years). A total of 5197 (3.7%) reported 1 or more incident fractures that occurred, on average, 1.5 years after recruitment. The characteristics of women with and without a fracture are shown in TABLE 1. The main factor affecting the incidence of fracture was a woman's age at recruitment; the proportion reporting any fracture was 3.2% at 50 to 54 years, 3.6% at 55 to 59 years, 4.3% at 60 to 64 years, and 4.8% at 65 to 69 years.

### Use of Hormone Therapy

TABLE 2 shows the reported incidence of any fracture and of hip fracture, by age and use of hormone therapy. Al-

though the total number of hip fractures is relatively small, among never users of hormone therapy the proportion reporting a hip fracture increased steeply with age: 0.04% for ages 50 to 54 years, 0.12% for 55 to 59 years, 0.17% for 60 to 64 years, and 0.24% for 65 to 69 years at baseline.

Compared with women who had never used hormone therapy, women who were currently using hormone therapy at the time of recruitment had a significantly lower incidence of fracture during the follow-up period (adjusted RR, 0.62; 95% CI, 0.58-0.66; $P<.001$) (FIGURE 1). The incidence of fracture among past users of hormone therapy at baseline did not differ significantly from that in never users (RR, 1.07; 95% CI, 0.99-1.15), even among women who had recently ceased use (Figure 1). There was no significant trend in the RR of fracture according to time since last use of hormone therapy in past users ($P$ for trend = .20).

Among current users of hormone therapy the RR of fracture was substantially reduced for all durations of use at baseline. The RR of fracture decreased with increasing duration of hormone therapy, at least up to 5 to 9 years of use (FIGURE 2), and a test for linear trend was statistically significant ($P=.001$). No significant reduction in the RR of fracture was found for past use of hormone therapy of any duration, and the trend with duration of use in past users was not significant ($P=.15$).

The results in Figures 1 and 2 remained similar when analyses were restricted to fractures occurring in the 12 months after recruitment, which occurred an average of 6.6 months after baseline recording of hormone therapy use. For current compared with never users of hormone therapy, the RRs of any fracture occurring in the 12 months after recruitment were as follows: 0.61 (95% CI, 0.54-0.68) overall; 0.71 (95% CI, 0.48-1.05) for use less than 1 year; 0.68 (95% CI, 0.57-0.81) for 1 to 4 years; 0.52 (95% CI, 0.43-0.62) for 5 to 9 years; and 0.61 (95% CI, 0.48-0.77) for 10 or more years of hormone therapy use at baseline. For past vs never users, the RRs of a fracture in the 12 months after recruitment were as follows: 0.98 (95% CI, 0.71-1.34) for use ceasing less than 1 year before recruitment; 0.99 (95% CI, 0.80-1.24) for use ceasing 1 to 2 years before recruitment; 1.05 (95% CI, 0.80-1.39) for use ceasing 3 to 4 years before recruitment; and 1.12 (95% CI, 0.92-1.37) for use ceasing 5 or more years before recruitment. The overall RR during the first 12 months of follow-up was 1.07 (95% CI, 0.95-1.22) for all past users.

The RRs in current and past users of hormone therapy were further adjusted for various other factors, including cigarette smoking, alcohol consumption, parity, previous use of oral contraceptives, and a history of certain illnesses at baseline (hypertension, venous thromboembolism, heart disease, stroke, diabetes, asthma, rheumatoid arthritis, osteoarthritis, or thyroid disease). There was little change in the magnitude of the estimated RR, with the additional adjustment resulting in RRs ranging from 0.61 to 0.62 for current use and 1.06 to 1.07 for past vs never users of hormone therapy. Results were not altered appreciably when women with a hysterectomy or who had begun hormone therapy before their

**Table 1.** Characteristics of Study Participants at Baseline*

| | No. (%) of Women | |
|---|---|---|
| | Reporting ≥1 Fracture (n = 5197) | Not Reporting Fracture (n = 133 540) |
| Age at recruitment, y | | |
| 50-54 | 1159 (22.3) | 35 135 (26.3) |
| 55-59 | 1885 (36.3) | 50 772 (38.0) |
| 60-64 | 1935 (37.2) | 43 267 (32.4) |
| 65-69 | 218 (4.2) | 4366 (3.3) |
| Age at menopause, y | | |
| <50 | 2545 (52.6) | 61 816 (49.9) |
| ≥50 | 2290 (47.4) | 62 004 (50.1) |
| Socioeconomic status† | | |
| Low | 2667 (52.7) | 65 114 (49.9) |
| High | 2391 (47.3) | 65 297 (50.1) |
| Medical history of certain illnesses‡ | | |
| Yes | 1911 (36.8) | 43 223 (32.4) |
| No | 3286 (63.2) | 90 317 (67.6) |
| Smoking | | |
| Current | 737 (15.0) | 19 662 (15.5) |
| Not current | 4189 (85.0) | 107 187 (84.5) |
| Alcohol | | |
| Drinks alcohol | 4246 (81.7) | 109 631 (82.1) |
| Does not drink alcohol | 951 (18.3) | 23 909 (17.9) |
| Strenuous physical activity | | |
| <1 Time per week | 2896 (57.3) | 75 209 (57.9) |
| ≥1 Times per week | 2156 (42.7) | 54 687 (42.1) |
| Body mass index§ | | |
| <25 | 2304 (46.6) | 61 486 (48.1) |
| ≥25 | 2635 (53.4) | 66 439 (51.9) |
| Parity | | |
| Parous | 4573 (88.2) | 117 746 (88.3) |
| Nulliparous | 609 (11.8) | 15 593 (11.7) |
| Oral contraceptive use | | |
| Ever | 2593 (50.4) | 68 990 (52.0) |
| Never | 2556 (49.6) | 63 629 (48.0) |

*Numbers do not always sum to totals due to missing values and percentages are calculated for women reporting characteristic.
†As defined by the deprivation index described in the "Methods" section.
‡Hypertension, heart disease, stroke, thromboembolism, diabetes, asthma, rheumatoid arthritis, osteoarthritis, or thyroid disease reported at baseline.
§Measured as weight in kilograms divided by the height in meters squared.

natural menopause were excluded from the analyses: the corresponding RRs of fracture in current and past vs never users of hormone therapy were 0.59 (95% CI, 0.55-0.64) and 1.06 (95% CI, 0.98-1.15), respectively.

### Type and Dose of Hormone Therapy

No significant variations in the relationship between use of hormone therapy and fracture incidence were observed according to the specific hormone currently being used (FIGURE 3). Compared with risk in never users, the overall RR of fracture was reduced to a similar extent in current users of estrogen only (RR, 0.64; 95% CI, 0.58-0.71), combined estrogen-progestin (RR, 0.58; 95% CI, 0.53-0.64), and other types of hormone therapy (RR, 0.67; 95% CI, 0.56-0.80) ($P=.19$).

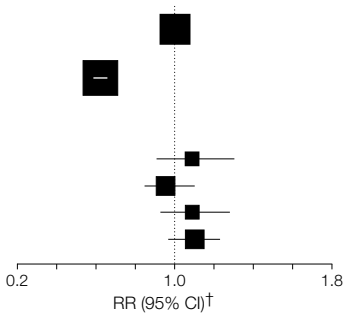
The RR of fracture among current users of tibolone (a nonhormonal preparation with estrogenic, progestagenic, and androgenic activities) was significantly lower than that in never users of hormone therapy (RR, 0.67; 95% CI, 0.54-0.83). The relationship between current use of hormone therapy and fracture incidence did not vary significantly according to the hormonal constituents of the estrogen (equine estrogen vs estradiol, $P=.30$) or progestin (norethisterone vs medroxyprogesterone acetate vs norgestrel/levonorgestrel, $P=.87$) currently used at recruitment. Fracture incidence also did not vary significantly according to the dose of estrogen currently being used (equine estrogen $<0.625$ vs $\geq 0.625$ mg, $P=.91$; oral estradiol $<1$ vs $\geq 1$ mg, $P=.69$; transdermal estradiol $<50$ vs $\geq 50$ µg, $P=.53$) (Figure 3). The RRs of fracture among current users of estrogen-only hormone therapy were 0.60 (95% CI, 0.53-0.68) for oral formulations, 0.75 (95% CI, 0.65-0.86) for transdermal agents, and 0.52 (95% CI, 0.34-0.80) for implants (Figure 3). There was weak evidence of heterogeneity between these routes of administration ($P=.04$), which did not appear to be accounted for by differences in duration of use of hormone therapy; however, given the large number of statistical tests conducted, this finding is difficult to in-

**Table 2.** Women Followed Up, Person-Years Accrued, and Fracture Incidence According to Age and Use of Hormone Therapy at Baseline

| | Use of Hormone Therapy at Baseline | | | |
|---|---|---|---|---|
| Age at Baseline, y | Current | Past | Never | All Women |
| 50-54 | | | | |
| No. followed up | 15 021 | 5282 | 15 991 | **36 294** |
| Person-years, in thousands | 41.7 | 14.5 | 44.1 | **100.4** |
| No. with hip/any fracture | 3/343 | 4/225 | 7/591 | **14/1159** |
| 55-59 | | | | |
| No. followed up | 20 075 | 9287 | 23 295 | **52 657** |
| Person-years, in thousands | 55.6 | 25.5 | 64.1 | **145.2** |
| No. with hip/any fracture | 14/531 | 9/402 | 29/952 | **52/1885** |
| 60-64 | | | | |
| No. followed up | 10 305 | 7167 | 27 730 | **45 202** |
| Person-years, in thousands | 28.6 | 19.7 | 76.2 | **124.5** |
| No. with hip/any fracture | 13/280 | 6/351 | 47/1304 | **66/1935** |
| 65-69 | | | | |
| No. followed up | 721 | 582 | 3281 | **4584** |
| Person-years, in thousands | 2.0 | 1.6 | 9.0 | **12.6** |
| No. with hip/any fracture | 0/25 | 1/30 | 8/163 | **9/218** |
| Total | | | | |
| No. followed up | 46 122 | 22 318 | 70 297 | **138 737** |
| Person-years, in thousands | 127.9 | 61.3 | 193.4 | **382.6** |
| No. with hip/any fracture | 30/1179 | 20/1008 | 91/3010 | **141/5197** |

**Figure 1.** Relative Risk (RR) of Incident Fracture in Relation to Recency of Hormone Therapy Use

| Use of Hormone Therapy at Baseline | Total Duration of Hormone Therapy Use at Baseline in Cases, Mean (SD), y | Cases/Population | RR* | RR (95% CI)† |
|---|---|---|---|---|
| Never Users | | 3010/70 297 | 1.00 | 1.00 |
| Current Users | 5.9 (4.3) | 1179/46 122 | 0.62 | 0.62 (0.58-0.66) |
| Past Users | | | | |
| Time Since Last Use, y | | | | |
| <1 | 4.7 (4.3) | 130/2904 | 1.09 | 1.09 (0.91-1.30) |
| 1-2 | 3.5 (3.8) | 250/6263 | 0.96 | 0.96 (0.85-1.10) |
| 3-4 | 2.4 (3.0) | 160/3525 | 1.09 | 1.09 (0.93-1.28) |
| ≥5 | 1.5 (2.5) | 301/6247 | 1.12 | 1.10 (0.97-1.23) |




The position of the squares represents the RR with size of data markers inversely proportional to the variance of the log RR, indicating the amount of statistical information available for that particular estimate. CI indicates confidence interval.
*Adjusted for age and region.
†Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity (see Table 1).

terpret. Among users of combined estrogen-progestin, there was no significant difference in the effect on fracture risk between those taking sequential (0.58; 95% CI, 0.52-0.65) and continuous (0.56; 95% CI, 0.48-0.67) preparations ($P=.71$).

### Participant Characteristics and Fracture Cause and Site

No significant variation in the RR of fracture in current compared with never users of hormone therapy was observed among women of different ages at recruitment, ages at menopause, time between menopause and starting hormone therapy, socioeconomic status, previous illness, smoking habits, alcohol consumption, body mass index, physical activity, parity, or previous use of oral contraceptives (FIGURE 4). More than 95% of the study participants are white, so any possible effect modification by race/ethnicity cannot be examined in this population.

Overall, of the 5197 women reporting 1 or more incident fractures, 4102 (79%) attributed their fracture to a fall, 146 (3%) to an automobile accident, 281 (5%) to some other accident, 105 (2%) were reported to have been found on radiography without the woman being aware of the fracture, and 563 (11%) reported that the fracture was due to multiple causes, that the fracture occurred in a way other than the options listed on the questionnaire, or reported no immediate reason for their fracture. There was weak evidence that the RR of fracture in current vs never users of hormone therapy varied according to the reported reason for the fracture ($P=.05$, FIGURE 5). The results in Figures 1 through 4 remained similar when analyses were restricted to fractures resulting from a fall (data not shown).

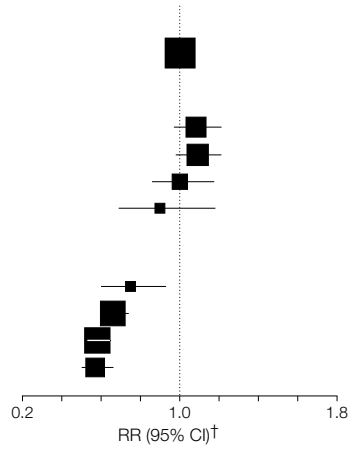
The 5197 women reported (in order of frequency) fractures of the wrist or arm (n=2557), ankle (n=1109), foot (n=616), leg (n=419), shoulder (n=241), spine (n=146), hip (n=141), hand (n=102), skull or face (n=93), chest or sternum (n=50), pelvis (n=54), and other or unknown sites (n=52). These numbers sum to more than 5197 because 336 women reported more than 1 incident fracture. Compared with never users, current users of hormone therapy at baseline had a lower risk of fracture at the most common fracture sites reported, although the RR varied significantly between the 7 specified fracture sites ($P<.001$, Figure 5). The lowest RR was for fracture of the wrist or arm (0.45; 95% CI, 0.40-0.50) and the RR for hip fracture associated with current use of hormone therapy was 0.62 (95% CI, 0.40-0.94). The RRs of fracture at different sites changed little when the analyses were restricted to fractures attributed to a fall. For example, in current vs never users of hormone therapy the RRs for wrist and hip fractures attributed to a fall were 0.45 (95% CI, 0.41-0.51) and 0.62 (95% CI, 0.40-0.94), respectively.

## COMMENT

Results from both randomized trials and observational studies have shown that use of hormone therapy protects against fracture.[1,2,9-14] In this large study population that included almost 140 000 postmenopausal women experiencing more than 5000 incident fractures, we have confirmed, but also extended, previous knowledge about the effect of hormone therapy on the incidence of fracture. In particular, we found a significantly reduced risk of fracture a year or so after women had started using hormone therapy , with the risk decreasing further with increasing duration of use. The magnitude of this protection did not differ materially according to which type of hormone a

**Figure 2.** Relative Risk (RR) of Incident Fracture in Relation to Recency and Duration of Hormone Therapy Use

| Duration of Hormone Therapy Use at Baseline | Total Duration of Hormone Therapy Use at Baseline in Cases, Mean (SD), y | Cases/Population | RR* | RR (95% CI)† |
|---|---|---|---|---|
| Never Users | | 3010/70 297 | 1.00 | 1.00 |
| Past Users | | | | |
| Total Duration of Use, y | | | | |
| <1 | 0.5 (0) | 363/8076 | 1.08 | 1.08 (0.97-1.21) |
| 1-4 | 2.0 (1.0) | 373/8186 | 1.09 | 1.09 (0.98-1.21) |
| 5-9 | 6.3 (1.4) | 171/3941 | 1.02 | 1.00 (0.86-1.17) |
| ≥10 | 12.4 (3.1) | 55/1334 | 0.94 | 0.90 (0.69-1.18) |
| Current Users | | | | |
| Total Duration of Use, y | | | | |
| <1 | 0.5 (0) | 81/2801 | 0.73 | 0.75 (0.60-0.93) |
| 1-4 | 2.7 (1.0) | 405/15 707 | 0.65 | 0.66 (0.60-0.74) |
| 5-9 | 6.8 (1.4) | 458/18 604 | 0.59 | 0.58 (0.53-0.65) |
| ≥10 | 12.8 (3.4) | 206/7956 | 0.60 | 0.57 (0.50-0.66) |



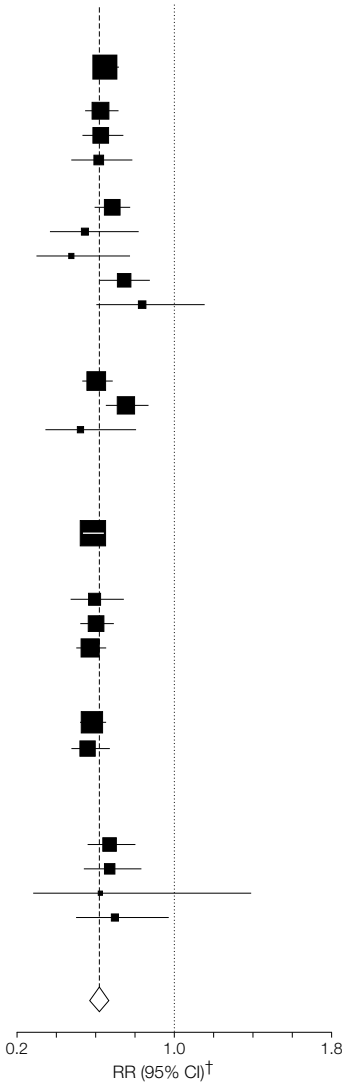

See the legend to Figure 1 for explanation of the data markers.
*Adjusted for age and region.
†Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity.

woman was currently using, or according to which specific estrogen or progestin or which dose was used. This study provides new evidence that the protective effect of hormone therapy on the risk of fracture wears off rapidly after use ceases and that this lack of protection does not vary significantly according to how long hormone therapy had been used previously. Although earlier studies have not generally found statistically significant reductions in the risk of fracture in past users of hormone therapy , the CIs around the risk estimates in other studies have been wide and so it was not possible beforehand to exclude modest persistent reductions in fracture incidence after use of hormone therapy had ceased.[10-14]

This study has a number of strengths. Data on use of hormone therapy were gathered prospectively and have been shown to provide a reliable measure of exposure to specific types, doses, and regimens of hormone therapy during the relevant follow-up period.[5,15] To avoid biases associated with differential prescribing of hormone therapy, analyses were restricted to postmenopausal women, those without cancer, and those who were not being treated for osteoporosis at baseline. To minimize potential confounding by other

**Figure 3.** Relative Risk (RR) of Incident Fracture for Current vs Never Users by Type of Hormone Therapy at Baseline

| Hormone Therapy Used at Baseline | Total Duration of Hormone Therapy Use at Baseline in Cases, Mean (SD), y | Current Users, Cases/Population | RR* | RR (95% CI)† |
|---|---|---|---|---|
| All Estrogen Only | 6.8 (4.6) | 513/19 189 | 0.65 | 0.64 (0.58-0.71) |
| All Equine Estrogen | 7.5 (5.0) | 219/8460 | 0.63 | 0.62 (0.54-0.71) |
| ≤0.625 mg | 7.4 (5.1) | 158/6025 | 0.63 | 0.62 (0.53-0.73) |
| >0.625 mg | 7.9 (4.7) | 61/2412 | 0.62 | 0.61 (0.47-0.78) |
| All Estradiol | 6.0 (3.8) | 244/8706 | 0.68 | 0.68 (0.59-0.77) |
| ≤1 mg Oral | 5.9 (4.8) | 23/1037 | 0.54 | 0.54 (0.36-0.81) |
| >1 mg Oral | 6.4 (5.0) | 16/844 | 0.47 | 0.47 (0.29-0.77) |
| ≤50 µg Transdermal | 5.8 (3.6) | 151/4921 | 0.74 | 0.74 (0.62-0.87) |
| >50 µg Transdermal | 6.7 (4.0) | 36/1072 | 0.84 | 0.83 (0.60-1.15) |
| By Formulation | | | | |
| Oral | 7.3 (5.0) | 290/11 546 | 0.61 | 0.60 (0.53-0.68) |
| Transdermal | 6.0 (3.7) | 197/6360 | 0.76 | 0.75 (0.65-0.86) |
| Implanted | 7.9 (5.3) | 21/976 | 0.53 | 0.52 (0.34-0.80) |
| All Estrogen-Progestin Combinations | 5.4 (4.0) | 539/22 472 | 0.58 | 0.58 (0.53-0.64) |
| By Progestin Constituent | | | | |
| Medroxyprogesterone Acetate | 4.4 (3.8) | 73/3027 | 0.58 | 0.59 (0.47-0.74) |
| Norethisterone | 4.7 (3.5) | 198/8094 | 0.59 | 0.60 (0.52-0.69) |
| Norgestrel/Levonorgestrel | 6.3 (4.0) | 256/10 890 | 0.57 | 0.57 (0.50-0.65) |
| By Type of Regimen | | | | |
| Sequential | 5.9 (3.9) | 364/15 192 | 0.58 | 0.58 (0.52-0.65) |
| Continuous | 4.4 (3.9) | 149/6411 | 0.56 | 0.56 (0.48-0.67) |
| All Other | 4.5 (3.4) | 127/4461 | 0.68 | 0.67 (0.56-0.80) |
| Tibolone | 4.8 (3.3) | 86/3037 | 0.67 | 0.67 (0.54-0.83) |
| Vaginal | 1.0 (1.2) | 6/221 | 0.62 | 0.62 (0.28-1.39) |
| Other/Not Known | 4.3 (3.6) | 35/1203 | 0.71 | 0.70 (0.50-0.97) |
| All Current Hormone Therapy | 5.9 (4.3) | 1179/46 122 | 0.62 | 0.62 (0.58-0.66) |




See the legend to Figure 1 for explanation of the data markers. The RR is for current hormone therapy users vs never users (3010 cases/70 297 population). The dashed line represents the overall RR (0.62) for all current users of hormone therapy vs never users at baseline.
*Adjusted for age and region.
†Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity.

factors, analyses were adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity. We examined for possible interaction between 11 personal characteristics and current use of hormone therapy in 22 subgroups, and we found no evidence of significant modification of the effect of hormone therapy by any of these factors.

The results presented here relate the pattern of hormone therapy use at baseline to incident fractures, which occurred an average of 1.5 years after the recording of baseline information. Hence, duration of current use of hormone therapy at the time of the event would be somewhat longer, on aver-

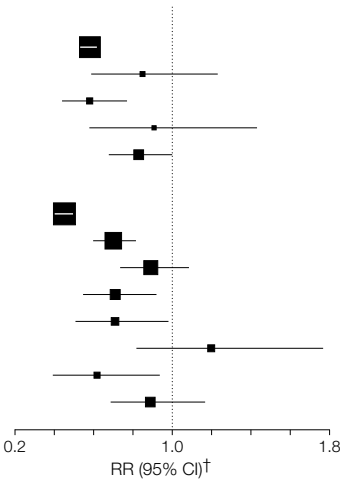
**Figure 4.** Effect of Current vs Never Use of Hormone Therapy on Risk of Incident Fracture Stratified by Participant Characteristics

| Characteristic at Baseline | Total Duration of Hormone Therapy Use at Baseline in Cases, Mean (SD), y | Cases in Current/Never Users | RR* | RR (95% CI)† |
|---|---|---|---|---|
| Age at Recruitment, y | | | | |
| <60 | 5.5 (4.0) | 874/1543 | 0.63 | 0.63 (0.58-0.69) |
| ≥60 | 7.0 (4.7) | 305/1467 | 0.59 | 0.59 (0.52-0.67) |
| Age at Menopause, y | | | | |
| <50 | 6.4 (4.5) | 611/1437 | 0.60 | 0.61 (0.55-0.67) |
| ≥50 | 4.7 (3.1) | 421/1496 | 0.61 | 0.61 (0.54-0.68) |
| Time Between Menopause and Starting Use of Hormone Therapy, y | | | | |
| <5 | 6.5 (4.6) | 807/3010 | 0.62 | 0.62 (0.57-0.67) |
| ≥5 | 3.8 (3.3) | 154/3010 | 0.77 | 0.73 (0.62-0.86) |
| Socioeconomic Status | | | | |
| Low | 5.8 (4.3) | 603/1571 | 0.65 | 0.65 (0.59-0.72) |
| High | 6.1 (4.2) | 547/1357 | 0.59 | 0.58 (0.52-0.64) |
| Medical History‡ | | | | |
| History of Certain Illnesses | 6.2 (4.5) | 424/966 | 0.64 | 0.63 (0.56-0.71) |
| No History of Certain Illnesses | 5.8 (4.1) | 755/2044 | 0.60 | 0.60 (0.55-0.65) |
| Smoking | | | | |
| Current | 6.1 (4.2) | 179/399 | 0.67 | 0.67 (0.56-0.80) |
| Not Current | 5.9 (4.2) | 949/2443 | 0.61 | 0.61 (0.56-0.66) |
| Alcohol Consumption | | | | |
| Drinks Alcohol | 5.9 (4.2) | 1000/2423 | 0.61 | 0.60 (0.56-0.65) |
| Does Not Drink Alcohol | 6.3 (4.7) | 179/587 | 0.67 | 0.68 (0.57-0.80) |
| Body Mass Index | | | | |
| <25 | 5.9 (4.1) | 567/1315 | 0.60 | 0.60 (0.54-0.66) |
| ≥25 | 6.0 (4.4) | 564/1532 | 0.64 | 0.64 (0.58-0.71) |
| Strenuous Physical Activity | | | | |
| <1 Time per Week | 5.9 (4.3) | 636/1688 | 0.62 | 0.61 (0.56-0.67) |
| ≥1 Times per Week | 5.9 (4.2) | 516/1230 | 0.62 | 0.62 (0.56-0.69) |
| Parity | | | | |
| Nulliparous | 5.8 (4.6) | 134/373 | 0.64 | 0.65 (0.53-0.79) |
| Parous | 6.0 (4.2) | 1040/2629 | 0.61 | 0.61 (0.57-0.66) |
| Oral Contraceptive Use | | | | |
| Ever | 5.8 (4.3) | 693/1311 | 0.59 | 0.59 (0.54-0.65) |
| Never | 6.1 (4.2) | 479/1674 | 0.66 | 0.66 (0.59-0.73) |
| All Current Hormone Therapy | 5.9 (4.3) | 1179/3010 | 0.62 | 0.62 (0.58-0.66) |


See the legend to Figure 1 for explanation of the data markers. The dashed line represents the overall RR (0.62) for all current users of hormone therapy vs never users at baseline.
*Adjusted for age and region.
†Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity.
‡Hypertension, heart disease, stroke, thromboembolism, diabetes, asthma, rheumatoid arthritis, osteoarthritis, or thyroid disease reported at baseline.

**Figure 5.** Relative Risk (RR) of Incident Fracture by Reported Fracture Cause and Site Among Current vs Never Users of Hormone Therapy

| Reported Cause and Site of Fracture | Total Duration of Hormone Therapy Use at Baseline in Cases, Mean (SD), y | Cases in Current/Never Users | RR* | RR (95% CI)† |
|---|---|---|---|---|
| Cause | | | | |
| Fall | 6.0 (4.3) | 863/2405 | 0.57 | 0.58 (0.53-0.62) |
| Automoblie Accident | 6.5 (4.2) | 47/83 | 0.86 | 0.85 (0.59-1.23) |
| Other Accident | 5.2 (3.6) | 72/168 | 0.60 | 0.58 (0.44-0.77) |
| Found on Radiography Only | 6.2 (4.0) | 33/54 | 0.94 | 0.91 (0.58-1.43) |
| Other‡ | 5.9 (4.3) | 164/300 | 0.85 | 0.83 (0.68-1.01) |
| Site | | | | |
| Wrist/Arm | 5.8 (4.2) | 429/1473 | 0.46 | 0.45 (0.40-0.50) |
| Ankle | 6.2 (4.5) | 253/579 | 0.69 | 0.70 (0.60-0.81) |
| Foot | 5.6 (4.0) | 184/311 | 0.88 | 0.89 (0.74-1.08) |
| Leg | 5.8 (3.9) | 87/204 | 0.71 | 0.71 (0.55-0.92) |
| Shoulder | 5.4 (4.1) | 56/127 | 0.71 | 0.71 (0.51-0.98) |
| Spine | 5.3 (3.7) | 50/64 | 1.24 | 1.20 (0.82-1.76) |
| Hip | 7.3 (4.1) | 30/91 | 0.63 | 0.62 (0.40-0.94) |
| Other/Unknown | 6.9 (5.0) | 90/161 | 0.88 | 0.89 (0.69-1.17) |




See the legend to Figure 1 for explanation of data markers.
*Adjusted for age and region.
†Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity.
‡Includes multiple and unspecified causes.

age, than the duration of current use recorded at baseline. However, the relationship between duration of use and other patterns of hormone therapy use and the risk of fracture did not change materially when analyses were restricted to fractures occurring within 12 months of recruitment, 6.6 months after the recording of baseline information. Response rates at follow-up did not vary substantially by age or by the pattern of hormone therapy at baseline, but they were greater in women of higher compared with lower socioeconomic status. Because the RR of fracture associated with the use of hormone therapy did not vary according to socioeconomic status, adjustment for this variable in all analyses should allow for the differential follow-up. It is unknown whether women who experienced a fracture were more or less likely than women who did not have a fracture to return a follow-up questionnaire. The fact that the age-specific annual incidence rates found for all fractures and for hip fractures are consistent with those reported in the Women's Health Initiative (WHI) trials,[1,2] both for women using and not using hormone therapy , suggests that differential response rates according to fracture history are unlikely to be a serious problem in this study.

Two thirds of the fractures analyzed here were of the wrist, arm, or ankle, and more than three quarters of all fractures resulted from a fall. Self-reporting of the types of fractures included in these analyses has been shown to be reliable, with approximately 90% being confirmed on radiography.[16,17] The finding of a rapid onset and offset of the effect of hormone therapy on fracture, along with the lack of any substantial difference in effect according to the type of hormone used, is in keeping with the effects of hormone therapy on bone mineral density.[1,18-20]

The RR of hip fracture in current vs never users of hormone therapy (0.62; 95% CI, 0.40-0.94) is consistent with that found in the WHI trials of hormone therapy.[1,2] The absolute incidence of hip fracture increased sharply with age (Table 2), and so use of hormone therapy at older, compared with younger, ages should result in a greater absolute reduction in fracture incidence. A typical pattern of hormone therapy use in this population, whereby a woman begins at around menopause (≈50 years) and continues for 5 years, is estimated to prevent 0.3 hip fractures per 1000 users, whereas 5 years' use beginning at age 60 years is estimated to prevent approximately 1 hip fracture per 1000 users. However, at these ages 5 years' use of hormone therapy would lead to a greater increase in the absolute incidence of breast cancer and of stroke than any reduction in the absolute incidence of hip fracture.[1,3,21,22] No data were available for women older than 70 years. Our finding of no protection against fracture in past users of hormone therapy suggests that at such ages, when the incidence of fracture of the hip becomes increasingly common, any previous use of hormone therapy is unlikely to provide residual protection against hip fracture.

**Author Contributions:** Drs Banks, Beral, and Reeves had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Banks, Beral, Reeves.
*Analysis and interpretation of data:* Banks, Beral, Reeves, Balkwill, Barnes.
*Drafting of the manuscript:* Banks, Beral, Reeves, Balkwill, Barnes.
*Critical revision of the manuscript for important intellectual content:* Banks, Beral, Reeves, Balkwill, Barnes.
*Statistical expertise:* Reeves, Balkwill, Barnes.
*Obtained funding:* Beral, Reeves.
The Million Women Study Coordinating Center staff and collaborating UK National Health Service Breast Screening Center staff were responsible for data acquisition.

**Million Women Study Steering Committee:** Joan Austoker, Emily Banks, Valerie Beral, Ruth English, Julietta Patnick, Richard Peto, Gillian Reeves, Martin Vessey (Chair), Matthew Wallis.

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**Collaborating UK National Health Service Breast Screening Centers:** Avon, Aylesbury, Barnsley, Basingstoke, Bedfordshire and Hertfordshire, Cambridge and Huntingdon, Chelmsford and Colchester, Chester, Cornwall, Crewe, Cumbria, Doncaster, Dorset, East Berkshire, East Cheshire, East Devon, East of Scotland, East Suffolk, East Sussex, Gateshead, Gloucestershire, Great Yarmouth, Hereford and Worcester, Kent (Canterbury, Gillingham, Maidstone), Kings Lynn, Leicestershire, Liverpool, Manchester, Milton Keynes, Newcastle, North Birmingham, North East Scotland, North Lancashire, North Middlesex, North Nottingham, North of Scotland, North Tees, North Yorkshire, Nottingham, Oxford, Portsmouth, Rotherham, Sheffield, Shropshire, Somerset, South Birmingham, South East Scotland, South East Staffordshire, South Derbyshire, South Essex, South Lancashire, South West Scotland, Surrey, Warrington Halton St Helens and Knowsley, Warwickshire Solihull and Coventry, West Berkshire, West Devon, West London, West Suffolk, West Sussex, Wiltshire, Winchester, Wirral and Wycombe.

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