Discontinuation of menopausal hormone therapy and risk of fracture: nested case–control studies using routinely collected primary care data

Yana Vinogradova, Barbara Iyen, Tahir Masud, Lauren Taylor, Joe Kai

Summary

Background Women benefit from reduced fracture risk while using menopausal hormone therapy. However, information on risks after stopping menopausal hormone therapy is scarce and inconsistent, with no information on longer-term fracture risk as women age. We aimed to produce robust estimates of fracture risk among past users for the longest possible period after discontinuing therapy.

Methods We did a nested case–control study using UK primary and secondary care data from the Clinical Practice Research Datalink, with the underlying cohorts CPRD GOLD and Aurum. Women, aged 40 years and older, registered with a primary care practice between Jan 1, 1998, and Feb 28, 2023, and with a first record for any fracture, were matched at the fracture index date with up to five female controls with no fracture history, who were of the same age and registered at the same general practice. Menopausal hormone therapy-related fracture risks were assessed using conditional logistic regression adjusted for demographics, family history, menopausal symptoms, comorbidities, and other medications.

Findings In total, 648 747 women (500 692 from Aurum and 148 055 from GOLD databases) with a first fracture record during the study period were matched to 2 357 125 women with no previous or contemporaneous fracture record. Age of average fracture cases was 68·5 years (SD 14·0), 3·2% were recorded as being from minority ethnic populations, and about a quarter of patients were older than 80 years. 140 410 (21·6%) cases used menopausal hormone therapy for a median of 3·6 years (IQR 1·3–6·8) and 515 917 (21·9%) controls used it for a median of 3·9 years (1·4–7·3). Compared with never-use, overall fracture risk was reduced for current use (oestrogen-only odds ratio [OR] 0·76 [95% CI 0·74–0·78], oestrogen–progestogen OR 0·75 [0·73–0·76]), became higher 1–10 years after discontinuation (oestrogen-only OR 0·99 [0·98–1·01], oestrogen–progestogen OR 1·06 [1·05–1·08]), but was again lower for more than 10 years post-cessation (oestrogen-only OR 0·93 [0·91–0·94], oestrogen–progestogen OR 0·95 [0·94–0·96]). Risk levels varied by menopausal hormone therapy type and by duration of treatment. Estimated extra fracture cases per 10 000 women-years 1–10 years after oestrogen–progestogen treatment were equivalent to 14 cases for less than 5 years menopausal hormone therapy exposure and five cases for 5 or more years of exposure. However, for more than 10 years after discontinuation, we estimated three fewer fracture cases for those on oestrogen–progestogen therapy for less than 5 years exposure and 13 fewer fracture cases for those with 5 or more years of exposure.

Interpretation We have observed an attenuation of fracture risk after discontinuing menopausal hormone therapy, which manifests after an initial sharp rise. Fracture risk generally increases with age, but after discontinuation of menopausal hormone therapy, fracture risk increases steeply, usually to above the levels of comparable never-users, and then rises less quickly relative to never-users to become again notably reduced by comparison in older age. Our findings provide information for researchers looking to improve fracture risk outcomes for women after discontinuing menopausal hormone therapy, and for doctors and their patients to consider before commencing or stopping menopausal hormone therapy, especially regarding expected steep post-discontinuation rises in fracture risk and periods of enhanced fracture risk.

Funding National Institute for Health & Care Research.

Lancet Healthy Longev 2025; 6: 100729

Published Online July 23, 2025 https://doi.org/10.1016/j.lanhl.2025.100729

Centre for Academic Primary Care, Lifespan & Population Health, School of Medicine, University of Nottingham, Nottingham, UK (Y Vinogradova PhD, B Iyen PhD, Prof J Kai MD); **Department of Geriatric Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK** (Prof T Masud MRCP); **Eastwood Primary Care Centre, Nottinghamshire, UK** (L Taylor BMBS)

Correspondence to: Yana Vinogradova, Centre for Academic Primary Care, Lifespan & Population Health, School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK **yana.vinogradova@nottingham.ac.uk**

Introduction

Bone mineral density decreases with age and can decrease more rapidly in women during the period of menopause. Among ageing populations, rising levels of osteoporosis and fractures have become major health-care, societal, and economic concerns.[1–3] Menopausal hormone therapy is a preferred treatment for menopause symptoms, and the beneficial effects on bone density and fracture risk while patients receive this therapy are well known.[4,5] Some studies have investigated bone health or fracture outcomes after menopausal hormone therapy has ceased, but existing findings are inconsistent, with a lack of long-term evidence.

Research in context

Evidence before this study

We searched PubMed for articles in English published between Jan 1, 1975, and Jun 30, 2024, for trials, observational studies, and meta-analyses with outcomes of any type of fracture or of bone mineral density change after exposure to menopausal hormonal therapy. We focused on studies with follow-up after discontinuation of menopausal hormone therapy intervention or treatment. Of the clinical trials found, only the Women's Health Initiative (5-year follow-up after trial end) provided fracture-risk evidence after menopausal hormone therapy discontinuation. Evidence from observational studies was inconsistent, with some reporting no changes and others reporting various rates of risk increase towards never-user levels. The few studies with post-cessation follow-up exceeding 5 years were not powered to deliver reliable risk estimates over the whole period or to identify differences between treatments.

Added value of this study

We used prospectively recorded general practice and hospital records of fractures, including all menopausal hormone therapy treatments commonly prescribed to UK National Health Service patients. The study was powered to investigate menopausal hormone therapy types and regimens, and to deliver robust risk estimates for up to 25 years after discontinuation. We confirm that women who discontinue menopausal hormone therapy experience increases in fracture risk. However, we also provide novel evidence that most women will then experience levels initially higher than those of comparable never-users, before comparative risk-level paths change again to the advantage of past menopausal hormone therapy users. Therefore, past-user fracture risk in later life again becomes notably lower than the never-user comparators. This post-cessation pattern is consistent across menopausal hormone therapy types and formulations, but with clinically important differences relating to treatment type and, more importantly, duration of past menopausal hormone therapy exposure.

Implications of all the available evidence

Although fracture risks in all women increase with age, our findings suggest some persistent beneficial effects on bone ageing among discontinued menopausal hormone therapy users, with a continuing attenuation of age-related decline relative to never-users, after an initial rapid post-cessation loss in bone strength. Women who survive into older age will benefit overall from reduced fracture risk, not only while using menopausal hormone therapy, but also after stopping therapy of any type. However, the post-cessation medium-term elevation of fracture risk compared with never-users has important clinical implications. We discuss the potential advantages and disadvantages of different regimens, contrasting the risk patterns to be expected from short-term or long-term use. Regarding the implications for women before initiating menopausal hormone therapy, we note the need for individualised discussions and, in some cases, bone health assessments. Biological research might be needed to underpin and better understand our results, but our findings might help to enhance clinical and patient decision making for the future of women's health.

A meta-analysis of randomised controlled trials of menopausal hormone therapy (dominated by the Women's Health Initiative, which followed-up women for up to 5 years after treatment) reported fracture risk decreases for current users but an unchanged risk post-discontinuation.[6,7] The Million Women Study, a large observational study that investigated fracture risks during and after menopausal hormone therapy, similarly reported decreased fracture risks in current users but found no reportable change post-cessation.[8] However, a US study of menopausal hormone therapy users reported a 55% rise in hip fracture risk after discontinuation, compared with current use.[9] A National Osteoporosis Risk Assessment study found that bone density was higher in longer-term menopausal hormone therapy users and, although bone density decreased post-discontinuation, remained high compared with never-users. However, the number of fracture events was insufficient to demonstrate risk differences for different combinations of duration and recency of menopausal hormone therapy use.[10] All studies had power limitations during follow-up. Other evidence on fracture risks after stopping menopausal hormone therapy is also inconsistent, underpowered, or based only on short-term menopausal hormone therapy use, despite about 40% of UK therapy users having a more than 5-year exposure.[11]

We aimed to investigate the relationship between the risk of any fracture in users of menopausal hormone therapy and recency and duration of past use, focusing on the period after stopping menopausal hormone therapy and into the medium-term and long-term future.

Methods

Study design and participants

We used the Clinical Practice Research Datalink (CPRD), supplemented by linked Hospital Episode Statistics admission data, Office of National Statistics mortality data, and Townsend deprivation data. CPRD is a UK National Health Service (NHS) primary care data resource, used worldwide for medical research. Data from CPRD are routinely collected and representative of the UK population, including symptoms, diagnoses, investigation results, therapy prescriptions, life-style records and demographics.[12]

Details of the study and analysis plan have been published.[13] We conducted two nested case–control studies using underlying cohorts from CPRD GOLD and Aurum.[14] We followed-up women, aged 40 years and older, registered

with a primary care practice between Jan 1, 1998, and Feb 28, 2023, with at least 10 years of practice records before inclusion and no record of previous fractures. Fractures were identified from general practice records using Read codes and from linked hospital and mortality data using ICD-10 codes. Cases—women with a first ever recorded any fracture—were matched at fracture index date with up to five controls, who were women with the same birth year, from the same practice, and who had no history of any fractures.

CPRD has obtained ethical approval from a National Research Ethics Service Committee. The CPRD Research Data Governance (RDG) application has been approved by the CPRD RDG committee (N 22_002376). A project summary is published on the CPRD website. CPRD data are anonymised research data and therefore written informed consent from included individuals was not required.

Procedures

We considered all menopausal hormone therapy prescriptions containing oestrogen and progestogen in the British National Formulary, section 6.4.1. Oral, transdermal, subcutaneous, or intra-uterine applications were considered systemic and vaginal applications were considered topical. For women with at least two prescriptions, we analysed two systemic exposures—oestrogen–progestogen for women with a uterus and oestrogen-only for women without. We analysed fracture outcomes in relation to duration of treatment and time since discontinuation, for all hormonal formulations commonly prescribed in NHS settings: oestrogens (oestradiol; and conjugated equine oestrogen) and progestogens (medroxyprogesterone acetate; norgestrel or levonorgestrel; norethisterone; and dydrogesterone). We also investigated oral and transdermal preparations for oestradiol, norgestrel or levonorgestrel, and norethisterone. Tibolone, topical oestrogens, raloxifene (prescribed to prevent menopausal osteoporosis), and single prescription menopausal hormone therapy use were included as confounders.

Statistical analysis

We estimated associations between fracture risk and exposure to menopausal hormone health using conditional logistic regression. For exposure, we categorised recency and durations and provided odds ratios (ORs) and 95% CIs. We used fractional polynomials to draw risk estimate patterns compared with never-use over the observational period (up to 25 years before the index date) by duration of exposure or time since discontinuation of treatment.[15]

Analyses were adjusted for confounders established as fracture-risk factors likely to have influenced doctors or patients in the decision to start, continue, or discontinue menopausal hormone therapy.[13] Selected confounders included patient characteristics, life-style measures, bone health and menopausal-related information, comorbidities, and other relevant medications if recorded before the index date. Potential confounders were included if their addition altered the OR for menopausal hormone therapy exposure by at least 1%.

Missing values for smoking status, alcohol consumption, and BMI were filled using multiple imputation techniques, creating five imputed datasets with multiple chained equations and making final estimates using Rubin's rules.[16] Because of higher levels of missing data, absent ethnicity information was classified as non-recorded.

Analyses were run separately on GOLD and Aurum data, and separate estimates were then combined using meta-analysis techniques with a fixed-effect model. The combined estimates are reported.[17] Incidence fracture rate in the non-exposed population was estimated by following up women from their study entry until first menopausal hormone therapy prescription or the point at which they left the study. Our combined estimates were then applied to calculate expected extra or fewer fractures in menopausal hormone therapy users.[18]

In sensitivity analyses, we addressed two possible biases. Information bias: some women might have registered with a practice long after their menopause and lack menopausal hormone therapy exposure data, so we analysed cases with fractures before age 80 years and their controls. Indication bias: women with known bone-related problems might have started menopausal hormone therapy treatment or switched to other bone-protective drugs (indications might include diagnoses of osteoporosis, osteomalacia, cancer, Paget's disease, alcoholism, HIV, or osteoporosis treatment medications recorded before the index date), so we analysed women with healthy bones.

Distinguishing fractures caused by low-density bones from trauma fractures would have been unreliable, because this level of detail was not consistently recorded. Therefore, we ran a subgroup analysis on cases diagnosed with fragility fractures (spine, hip, humerus, rib, radius or ulna, or pelvic) and their controls. Because site-specific risks might be affected differently by hormonal treatment, we also ran subgroup analyses for the most common sites (spine, hip, or humerus).

Bone density reduces with age, and obesity is associated with both increased fracture risk and faster bone loss, so we analysed three age categories with sufficient exposures to ensure reliability of findings (50–59, 60–69, and 70–79 years) and also analysed menopausal hormone therapy exposure and fracture risks for three BMI categories (up to 25 , 25–29, and $\geq$30 kg/m^2).[19] We used a 1% significance level to allow for multiple comparisons but reported 95% CIs to facilitate comparison with other studies. All statistical analyses were done with Stata (version 18).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

For the **project summary** see https://www.cprd.com/approved-studies/use-menopausal-hormone-therapy-and-risk-fractures-nested-case-control-study-using

Results

See Online for appendix

Overall, 648 747 women (Aurum, 500 692 and GOLD, 148 055) with a first fracture record during the study period were matched to 2 357 125 women with no previous or contemporaneous fracture record (appendix p 2). Descriptive statistics of included confounders for cases and controls across both datasets are presented in table 1. These data are presented separately for GOLD and Aurum in the appendix (pp 3–5) showing consistency but slightly higher prevalence for comorbidities and medication use in the GOLD dataset.

Average fracture age for cases was 68·5 years (SD 14·0); 3·2% were recorded as being from minority ethnic populations, with about a quarter of patients older than 80 years. Cases were more likely than controls to be current smokers (14·6% *vs* 12·6%) and to have higher prevalence for comorbidities and exposure to other medications.

Across both datasets, 140 410 cases (21·6%) and 515 917 controls (21·9%) had at least two menopausal hormone therapy prescriptions, with median exposures of 3·6 years (IQR 1·3–6·8) for cases and 3·9 years (1·4–7·3) for controls. 53 030 (37·8%) of the 140 410 casses exposed and 211 591 (41·0%) of the 515 917 controls had exposures of 5 or more years, and 14 608 (10%) of cases and 63 328 (12·3%) of controls had exposures of more than 10 years. Overall, 44 314 (6·8%) cases and 160 178 (6·8%) controls had used oestrogen-only therapy, and 96 096 (14·8%) cases and 355 739 (15·1%) controls had used oestrogen–progestogen therapy. During the observational period, 7568 (1·2%) cases and 29 347 (1·2%) controls had switched from oestrogen–progestogen to oestrogen-only therapy. Overall, 25 650 (4·0%) cases and 108 560 (4·6%) controls had a prescription within 1 year before the index date (current use), 60 609 (9·3%) cases and 199 767 (8·5%) controls discontinued between 1 year and 10 years before the index date, and 54 151 (8·3%) cases and 207 590 (8·8%) controls stopped more than 10 years before the index date.

Menopausal hormone therapy users were generally younger and less likely to be from a minority ethnic group and had more records for anxiety (among users, about 24% of cases and about 21% of controls; among non-users, about 16% of cases and about 14% of controls) and prescriptions for antidepressants, proton-pump inhibitors, sedatives, or systemic corticosteroids (appendix pp 6–8).

Overall, compared with never-use, current menopausal hormone therapy use was associated with lower fracture risk (oestrogen-only: OR 0·76 [95% CI 0·74–0·78]; oestrogen–progestogen: 0·75 [0·73–0·76]), discontinuation between 1 year and 10 years before with higher fracture risk (oestrogen-only 0·99 [0·98–1·01]; oestrogen–progestogen 1·06 [1·05–1·08]), and discontinuation more than 10 years before with decreased fracture risk (oestrogen-only: 0·93 [0·91–0·94]; oestrogen–progestogen: 0·95 [0·94–0·96]) (appendix pp 9–10).

A consistent pattern of fracture risks (compared with never-use of menopausal hormone therapy) for different therapies and hormone formulations over the years

	Cases (n=648 747)	Controls (n=2 357 125)
Age, years	68·5 (14·0)	68·0 (13·5)
Ethnicity		
White	532 039 (82·0%)	1 833 001 (77·8%)
Not recorded	96 245 (14·8%)	432 186 (18·3%)
Bangladeshi	575 (0·1%)	2819 (0·1%)
Black African	1553 (0·2%)	7845 (0·3%)
Caribbean	2723 (0·4%)	16 972 (0·7%)
Chinese	754 (0·1%)	4607 (0·2%)
Indian	6287 (1·0%)	22 303 (0·9%)
Other	4472 (0·7%)	19 732 (0·8%)
Other Asian	1925 (0·3%)	8464 (0·4%)
Pakistani	2174 (0·3%)	9196 (0·4%)
Townsend score quintile*		
1 (most affluent)	135 579 (20·9%)	508 689 (21·6%)
2	137 993 (21·3%)	511 696 (21·7%)
3	143 176 (22·1%)	518 777 (22·0%)
4	133 016 (20·5%)	474 834 (20·1%)
5 (most deprived)	98 983 (15·3%)	343 129 (14·6%)
BMI, kg/m^2		
Recorded	562 918 (86·8%)	2 016 073 (85·5%)
Mean (SD)	26·6 (5·9)	27·4 (6·0)
Smoking		
Recorded	616 416 (95·0%)	2209 976 (93·8%)
Non-smoker	369 868 (57·0%)	1 407 322 (59·7%)
Ex-smoker	151 512 (23·4%)	506 604 (21·5%)
Light (1–9 cigarettes per day)	50 314 (7·8%)	157 754 (6·7%)
Moderate (10–19)	28 541 (4·4%)	92 040 (3·9%)
Heavy (≥20)	16 181 (2·5%)	46 256 (2·0%)
Alcohol		
Recorded	562 025 (86·6%)	2 007 080 (85·1%)
Non-drinker	85 273 (13·1%)	304 294 (12·9%)
Trivial (< 1 unit per day)	322 815 (49·8%)	1 189 170 (50·5%)
Light (1–2)	100 855 (15·5%)	345 500 (14·7%)
Moderate (3–6)	43 377 (6·7%)	142 162 (6·0%)
Heavy (7–9)	5598 (0·9%)	15 088 (0·6%)
Very heavy (≥10)	4107 (0·6%)	10 866 (0·5%)
Chronic conditions		
Alcoholism	12 575 (1·9%)	22 204 (0·9%)
Anxiety	116 028 (17·9%)	365 827 (15·5%)
Breast cancer	29 358 (4·5%)	91 857 (3·9%)
Cancer (at any other site)	28 113 (4·3%)	87 580 (3·7%)
Cardiovascular disease	109 703 (16·9%)	324 912 (13·8%)
Chronic obstructive pulmonary disease	35 556 (5·5%)	86 232 (3·7%)
Dementia	15 020 (2·3%)	27 790 (1·2%)
Diabetes	61 263 (9·4%)	202 545 (8·6%)
Liver disease	9625 (1·5%)	27 881 (1·2%)
Rheumatoid arthritis	18 673 (2·9%)	46 290 (2·0%)
Bone-related conditions		
Osteoporosis	48 654 (7·5%)	104 172 (4·4%)
Family history of osteoporosis	5356 (0·8%)	16 054 (0·7%)
Other characteristics		
Early menopause	69 959 (10·8%)	228 971 (9·7%)
Hysterectomy	125 327 (19·3%)	433 713 (18·4%)

(Table 1 continues on next page)

	Cases (n=648 747)	Controls (n=2 357 125)
(Continued from previous page)		
Menopausal symptoms	140 816 (21·7%)	503 114 (21·3%)
Oophorectomy	29 380 (4·5%)	102 019 (4·3%)
Single menopausal hormone therapy prescription	36 307 (5·6%)	114 909 (4·9%)
Any use of other medications before the index date		
Antidepressants	140 816 (21·7%)	503 114 (21·3%)
Antiparkinsonians	4941 (0·8%)	10 689 (0·5%)
Antipsychotics	8383 (1·3%)	18 640 (0·8%)
Anxiolytics	61 218 (9·4%)	163 483 (6·9%)
Combined oral contraceptives	89 260 (13·8%)	342 552 (14·5%)
Proton-pump inhibitors	106 842 (16·5%)	306 170 (13·0%)
Sedatives	33 367 (5·1%)	83 515 (3·5%)
Systemic corticosteroids	85 063 (13·1%)	229 867 (9·8%)
Bone-related prescriptions		
Any osteoporotic drugs†	34 842 (5·4%)	76 668 (3·3%)
Bisphosphonates	34 734 (5·4%)	76 419 (3·2%)
Calcium	34 726 (5·4%)	85 550 (3·6%)
Vitamin D	22 858 (3·5%)	50 242 (2·1%)

Data are n (%) or mean SD. *Taken from individual records for linked practices, otherwise from practice area deprivation levels. †Any osteoporotic drugs include bisphosphonates, denosumab, and teriparatide.

Table 1: **Descriptive statistics recorded at the index date for fracture cases and their matched controls (combined AURUM and GOLD databases)**

after discontinuation of menopausal hormone therapy (zero years corresponds to current use) was shown (figure 1). Risk did not long stay decreased but rose quickly to become somewhat increased, before falling to reach equivalence, and then again showed a decrease, compared with never-use. Longer-term decreases appeared proportional to the duration of use for both therapy types in most recency categories (appendix p 11).

Compared with never-use, fracture risks after discontinuation varied by period of menopausal hormone therapy use. Data for different categories of recency and exposure are presented in figure 2. In women still on menopausal hormone therapy or those who stopped within a year of the index date, longer use of more than 10 years was associated with the lowest risk (oestrogen-only, OR 0·62 [95% CI 0·59–0·65]; oestrogen–progestogen, 0·66 [0·62–0·69]). For women who discontinued between 1 year and 10 years before the index date, the shorter the therapy, the higher the increase in risk after discontinuation, with risk staying similar to never-users only among women exposed to menopausal hormone therapy for more than 10 years.

Estimates for fracture risks (compared with same-aged never-users) by therapy type and years since menopausal hormone therapy discontinuation for short-term (<5 years) and long-term (≥5 years) use are shown in figure 3. In the first year after discontinuation, initial fracture-risk rate increases are greater for long-term than short-term use: oestrogen-only long-term, 36% versus short-term, 12%; oestrogen–progestogen long-term, 65% versus short-term, 29%. Overall, longer-term use was associated with lower risk profiles than shorter use.

Medians for durations of menopausal hormone therapy use and associated fracture risks for different types, formulations, and mode of delivery are presented in the appendix (pp 12–14) and demonstrated similar patterns. A flatter post-discontinuation risk curve for oestradiol–dydrogesterone, with a lesser decrease in risk for current use and almost no increased risk after discontinuation is shown in figure 1. This might be explained by the relatively low number of oestradiol–dydrogesterone long-term users because, when separated from short-term users, long-term oestradiol–dydrogesterone use demonstrates a reduced risk level (OR 0·67 [95% CI 0·58–0·76]) similar to other oestrogen–progestogen preparations (appendix p 13).

Results from sensitivity analyses, addressing possible information and indication biases, matched the main analysis (appendix p 15). Fragility fractures had slightly lower risks across all categories of exposures, but risk increases after discontinuation were sharper than in the main analysis, both across treatments and exposure terms (appendix p 16). Fracture risks for spine, hip, and humerus were similar (appendix p 17).

Additional analyses for age categories all had similar findings, with slight differences probably arising from higher average exposure durations and times since discontinuation at older ages (appendix p 18). The different BMI categories also revealed similar findings, with slightly lower risks in current long-term users for women with a lower BMI (appendix p 19).

For the study period, using both GOLD and Aurum cohorts, the incidence rate for a first fracture in unexposed women aged 40 years to 100 years was 142 fractures per 10 000 women-years. For short-term (<5 years) and long-term (≥5 years) use, the number of expected extra or fewer incident fractures among women using oestrogen-only or oestrogen–progestogen therapies for current use (including first year post-cessation) and for the key post-discontinuation periods is presented in table 2.

Compared with never-users, we expect fewer cases among current users: for short-term use, we expect 23 fewer cases per 10 000 women-years for those on oestrogen-only therapy, and 12 fewer cases per 10 000 women-years for those on oestrogen–progestogen therapy; for long-term use, we expect 45 fewer cases per 10 000 women-years for those on oestrogen-only therapy, and 48 fewer cases for those on oestrogen–progestogen therapy. Post-discontinuation—between 1 year and 10 years after—we expect more cases among past users (apart from long-term oestrogen-only users, for which we expect six fewer cases). In the short term, we expect nine more cases for those on oestrogen-only therapy and 14 more cases for those on oestrogen–progestogen therapy and for the long term, we expect five more cases for those on oestrogen–progestogen therapy. At more than 10 years post-discontinuation, we expect fewer cases among past users.

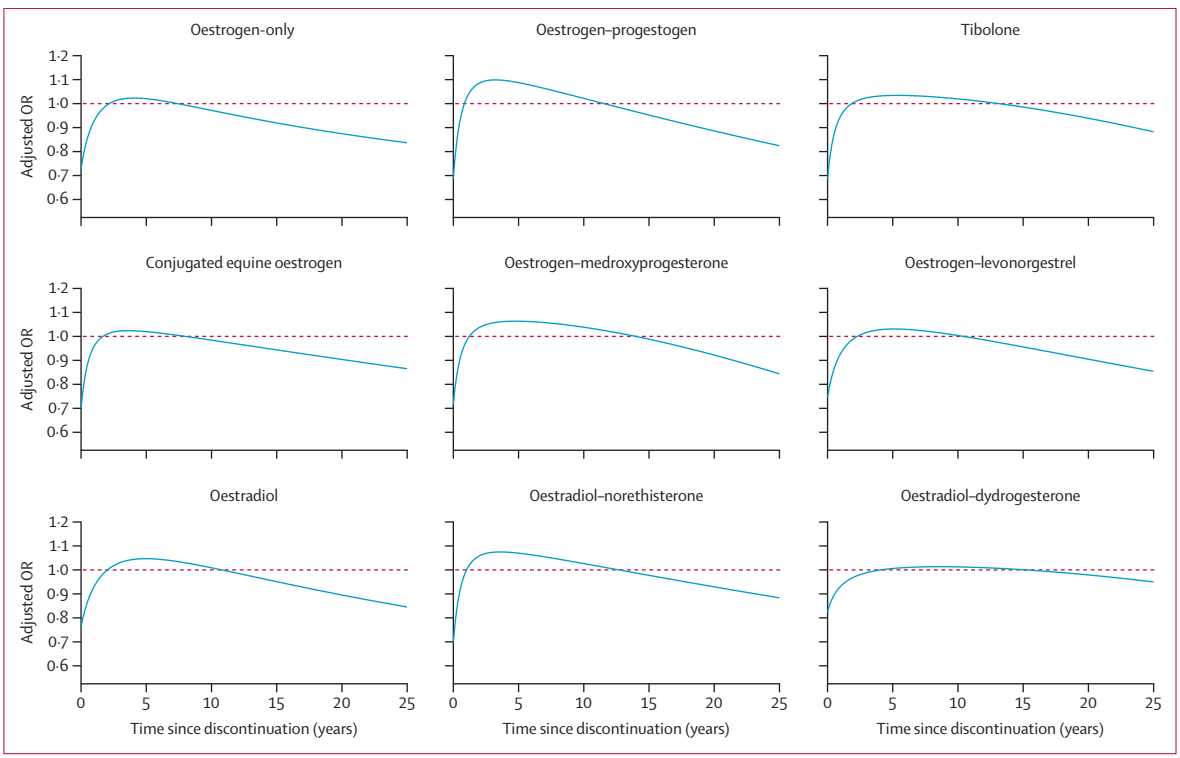

Figure 1: **Overall fracture risk patterns after menopausal hormone therapy discontinuation by treatment type**
ORs are adjusted for smoking, alcohol consumption, BMI, ethnicity, family history of osteoporosis, oophorectomy or hysterectomy, records of menopause, comorbidities, other medications, and number of years of data. Cases are matched to controls by age, general practice, and index date. The model includes fractional polynomial terms: oestrogen only (power −0·5 0); oestrogen–progestogen (power −2 1); tibolone (power −2 2); conjugated equine oestrogen (power −2 1); oestrogen–medroxyprogesterone (power −2 2); oestrogen–levonorgestrel (power −1 1); oestradiol (power −1 1); oestradiol–norethisterone (power −2 1); oestradiol–dydrogesterone (power −1 2). OR=odds ratio.

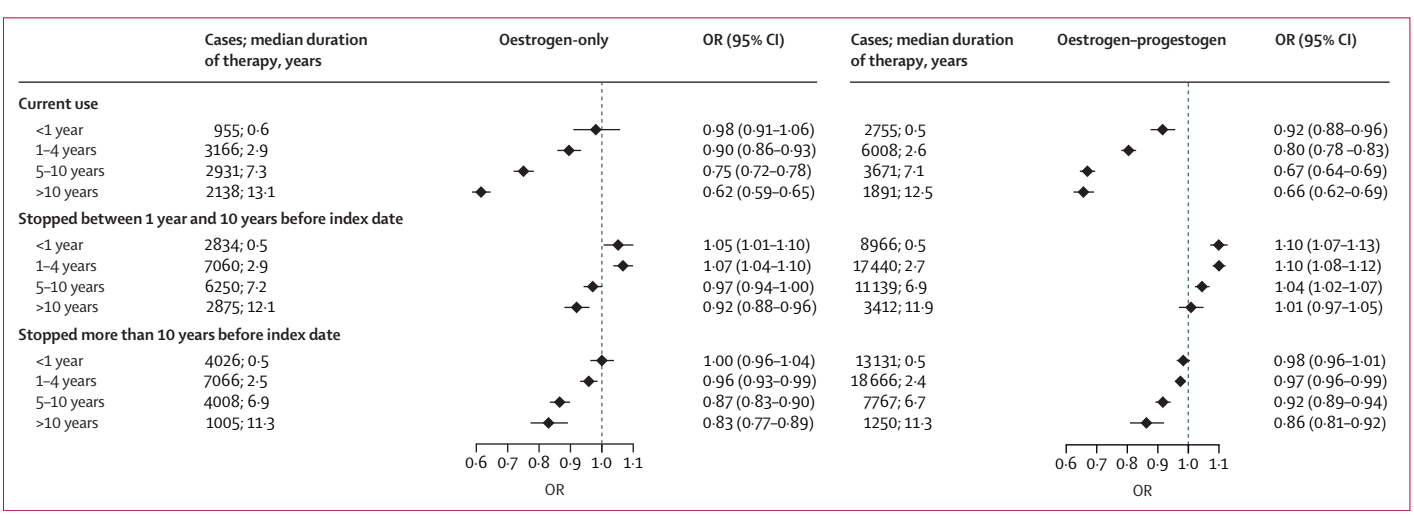

Figure 2: **Overall fracture risks by recency and duration of menopausal hormone therapy use and type**
ORs are adjusted for smoking, alcohol consumption, BMI, ethnicity, family history of osteoporosis, oophorectomy or hysterectomy, records of menopause, comorbidities, other medications, and number of years of data. Cases are matched to controls by age, general practice, and index date. Current use is defined as use within 1 year before the index date. OR=odds ratio.

For the short term, we expect four fewer cases for those on oestrogen-only therapy and three fewer cases for those on oestrogen–progestogen therapy and for the long term, we expect 20 fewer cases for those on oestrogen-only therapy and 13 fewer cases for those on oestrogen–progestogen therapy.

Diagrammatically, figure 4 presents estimated fracture risk paths for the average woman starting menopausal

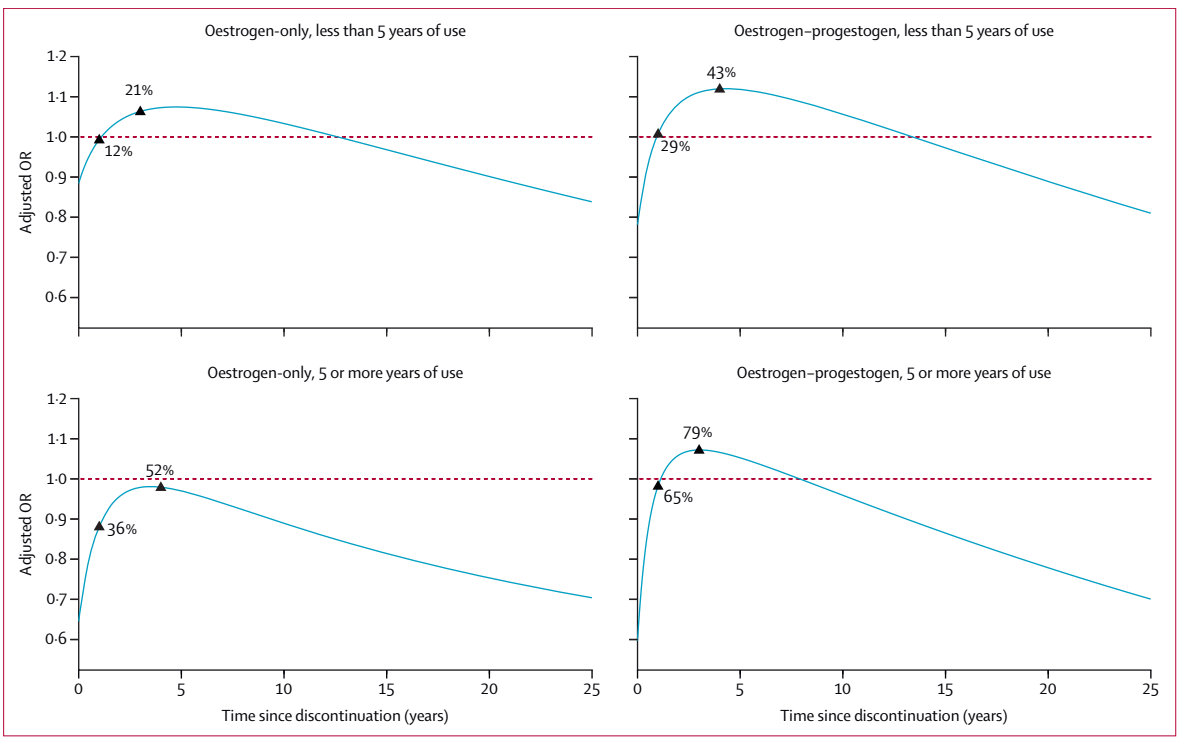

Figure 3: **Overall fracture risk patterns after menopausal hormone therapy discontinuation by therapy type and exposure to treatment**
Percentage markers at 1 year and 3 years show proportion of risk increase from the risk in current users. ORs are adjusted for smoking, alcohol consumption, BMI, ethnicity, family history of osteoporosis, oophorectomy or hysterectomy, records of menopause, comorbidities, other medications, and number of years of data. Cases are matched to controls by age, general practice, and index date. The model includes fractional polynomial terms: oestrogen-only, less than 5 years (power 0 0·5), 5 years or more (power –0·5 0); oestrogen–progestogen, less than 5 years (power –1 1), 5 years or more (power –2 1). OR=odds ratio.

	Oestrogen-only	Oestrogen–progestogen
Current use		
Used for less than 5 years	–12 (–17 to –7)	–23 (–26 to –20)
Used for 5 years or more	–45 (–48 to –41)	–48 (–50 to –45)
Stopped 1–10 years ago		
Used for less than 5 years	9 (5 to 13)	14 (12 to 17)
Used for 5 years or more	–6 (–10 to –3)	5 (2 to 8)
Stopped more than 10 years ago		
Used for less than 5 years	–4 (–7 to 0)	–3 (–5 to –1)
Used for 5 years or more	–20 (–24 to –16)	–13 (–16 to –9)

Data are differential numbers (95% CI) per 10 000 women-years. Incidence rate of first fracture for women between age 40 years and 100 years (inclusive) was 142 per 10 000 women-years. Negative numbers indicate fewer fractures.

Table 2: **Number of extra fractures expected from menopausal hormone therapy use**

hormone therapy at the age of about 51·5 years and continuing treatment for short-term or long-term duration. Post-discontinuation, longer-term use initially results in a more severe increase in fracture risk, but later shows a more-attenuated rise in fracture risks compared with shorter-term use. By contrast, the shorter-term use post-discontinuation path has a smaller initial rebound and, although subsequently having a less-attenuated fracture risk increase, importantly commences at an earlier stage of lower risk.

Discussion

To our knowledge, this study is the largest to date to investigate fracture risks in women after menopausal hormone therapy discontinuation, and might also have spanned the longest follow-up period of up to 25 years. We observed consistent patterns of a sharp risk increase soon after discontinuation, followed by a peak in most cases at levels higher than those among comparable never-users of menopausal hormone therapy, and then declining risk levels which were lower than never-user comparators, with risk magnitudes at all stages also dependent on the type and duration of therapy.

The Women's Health Initiative post-trial study followed-up 15 187 women for 5 years but revealed no increased fracture risk after discontinuation (conjugated equine oestrogen, hazard ratio [HR] 0·85 [95% CI 0·73–0·98]; conjugated equine oestrogen with medroxyprogesterone, HR 0·97 [0·87–1·09]),[7] possibly explained in part by the participants' relatively long exposures to menopausal hormone therapy (making their results and our long-exposure estimates more comparable). In the Million Women observational study, fracture risk for 841 past users with incident

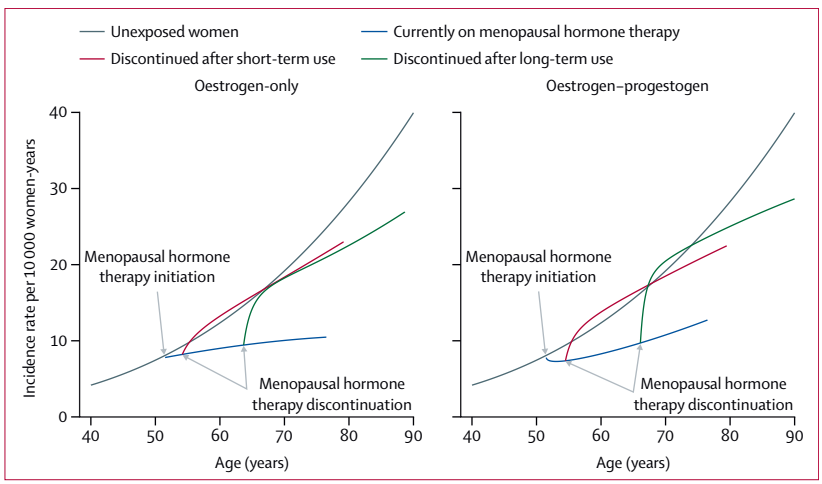

Figure 4: **Incidence rate of any fracture by age in women never exposed to menopausal hormone therapy and exposed from the average age of 51·5 years**
Short-term use was defined as less than 5 years. Long-term use was defined as 5 years or more.

fractures appeared higher than in never-users (relative ratio 1·07 [95% CI 0·99–1·15]), but lacked statistical significance and was not discussed.[8]

The American National Osteoporosis Risk Assessment programme followed-up 140 584 women for 10 years, of whom 269 had incident hip fractures. Within 5 years of menopausal hormone therapy discontinuation, they reported an elevated fracture risk compared with never-use, but only similar risks for the second 5-year period.[10] These results are similar to our relative risk findings, but their numbers of fracture events in short-term and long-term exposure categories were too low to compare with our findings.

Furthermore, in line with our findings, Karim and colleagues' study[9] investigated bone mineral density and hip fractures in encoded medical records (N=80 955, 12 468 menopausal hormone therapy discontinuations during the 6·5-year study period), reporting decreasing bone mineral density and a 55% increased risk of fracture compared with current users 2 years after discontinuation. However, Karim and colleagues' study did not distinguish between different menopausal hormone therapy exposures. Other smaller post-cessation fracture studies, such as the E3N cohort[20] and Danish Nurse[21] cohort studies, have lacked the requisite power or continuity of available data to deliver longer-term or robust detailed findings.

Similar (size and power) and other (cost and complexity) issues arise in studies of bone loss associated with menopausal therapy use, with or without an associated fracture analysis. The cost and complexity of biological data collection methods limit both the number of participants and frequency of measurements. Saarelainen and colleagues'[22] bone loss and wrist fracture study noted remaining uncertainty about bone loss after menopausal hormone therapy withdrawal and the need for long-term studies of bone mineral density changes following discontinuation of treatments. Such studies have often been limited by one or more of: data imbalance towards current menopausal hormone therapy usage; categorisation at the data collection stage leading to loss of information and uncertainty around follow-up periods; and participant selection issues or low numbers or high drop-out rates, leading to biases.[22–24]

Long-term bone health studies are complex to initiate and difficult to manage over time, and unlikely to be attempted in the absence of any clear rationale. The investigation of bone health after menopausal hormone therapy discontinuation would be useful to seek better understanding of observed fracture risk outcomes.

Our prospectively recorded general practice and hospital data facilitated identification of most fractures and was an important source of information for confounder adjustment and included all treatments commonly prescribed to UK NHS patients. The samples were representative of the general UK female population (for both menopausal and postmenopausal women),[12] and the study power delivered robust fracture risk estimates of specific treatment types and regimens for up to 25 years after discontinuation of menopausal hormone therapy.

In the UK, referral for a bone mineral density scan requires previous fracture-related clinical evidence or a fracture risk assessment (Frax or QFracture).[25] Bone mineral density information was also not consistently encoded, so this population-representative study was necessarily based on a fracture outcome.

Reliable information for physical activity, education, and diet was not available, but we adjusted findings by social deprivation score, ethnicity, BMI, alcohol consumption, and smoking status. A small proportion of these proxies were not recorded, requiring multiple imputation. However, for ethnicity, 15% of cases and 18% of controls lacked encoded records so were analysed as not recorded. Adjusting for ethnicity changed the OR by about 1% and the proportions of cases and controls with ethnicity not recorded were similar, suggesting that this data limitation might not have appreciably affected our results.

There was some uncertainty in our data regarding the cause of fracture, so the magnitudes of our estimates of fracture risk associated with menopausal hormone therapy are likely to be conservative. However, our analysis of fragility fractures, commonly connected to osteopenia, showed lower risks for current users and sharper risk increases after discontinuation of menopausal hormone therapy, further underlining the strength of our observations. Onset of menopause was not reliably recorded, but we included all available information on menopausal symptoms. However, some residual confounding always remains, despite design rigour.

The observed increases in risk to levels often higher than for never-users after discontinuation of menopausal hormone therapy reflect a similar rebound effect when denosumab (an anti-resorptive) is discontinued and increases in bone resorption raise concerns about fractures.[26] However, the subsequent persistent attenuation of age-related rising fracture risk among users who discontinued menopausal

hormone therapy compared with never-users, is novel and unexpected. We have investigated other possible factors, such as patient characteristics, to explain these results, but have found no conclusive associations. We therefore suspect that the results might reflect a previously unobserved outcome of menopausal hormone therapy use which, in the longer term post-discontinuation, slows progressive decline in bone strength.

One of the most notable findings of the study is the contrasting fracture risk paths which illustrates the difference between short-term and long-term menopausal hormone therapy use. Although short-term use might give a lower level of protection overall and, post-cessation, a weaker long-term attenuation of rising fracture risk, stopping menopausal hormone therapy at an earlier age means that the initial return to the norm is less severe and the subsequent excess risk period occurs over a lower-risk age period. There appears to be a trade-off between this smoother, less-attenuated risk path and the more changeable longer-term use path, which includes a more extreme risk rise immediately after discontinuation.

Our study suggests that, even after stopping menopausal hormone therapy, women could benefit from notably reduced fracture risk in older age. This likelihood holds for those who might have used menopausal hormone therapy for shorter periods because of concerns such as breast cancer. The study also suggests that women at higher fracture risk could possibly be helped to manage the transition from discontinuation through risk rebound, to the end of any period of excess risk. Such women could include those with known fracture risk factors before starting menopausal hormone therapy[27] and those who have used the therapy (particularly combined oestrogen–progestogen formulations) for longer durations. Possible topics for clinical research could include tapered, rather than sudden, cessation of menopausal hormone therapy or other bone health treatments.

Menopausal hormone therapy is widely the treatment of choice for managing menopause symptoms, but existing guidance has been unable to indicate, after discontinuation, long-term fracture-risk outcomes or reliable estimates of relative fracture risk change by type or regimen of therapy.[4,28,29] Our study delivers this information and, given longer life expectations and fracture risk increasing with age, should encourage further research both to improve the safety and utility of menopausal hormone therapy treatments and counter the potential personal and social burdens.

Contributors

YV initiated the study, undertook the original literature review, designed the study, drafted the original study protocol, organised the extraction of Clinical Practice Research Datalink data, did the analysis, and produced all manuscript drafts. YV and JK collaborated on revisions and refinement of the text. BI and YV accessed and verified data. TM provided expertise on fractures and osteoporosis including development of medical code lists. BI, JK, and LT advised on clinical aspects related to primary care and interpretation of the results. All coauthors critically reviewed the paper and approved the submitted version. YV is the guarantor of the study. YV and BI had access to the confidential data and all other authors provided clinical expertise. All authors accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Access to Clinical Practice Research Datalink (CPRD) data is subject to a licence agreement and protocol approval via CPRD's Research Data Governance Process. A guide to access is provided on the CPRD website.

For **CPRD information** see https://www.cprd.com/how-access-cprd-data

Acknowledgments

This study is funded by the National Institute for Health and Care Research (NIHR) School for Primary Care Research (project reference 617). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. This study is based in part on data from the CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. The Hospital Episode Statistics data used in this analysis are reused with permission of NHS Digital, which retains the copyright for those data. We thank the Office for National Statistics (ONS) for providing data on mortality. The ONS and NHS Digital bear no responsibility for the analysis or interpretation of the data. Finally, we are grateful to all practices contributing to CPRD and those patients who permitted their anonymised routine NHS data to be used for this research.

References

1 Rozenberg S, Al-Daghri N, Aubertin-Leheudre M, et al. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? *Osteoporos Int* 2020; **31:** 2271–86.
2 Stepan JJ, Hruskova H, Kverka M. Update on menopausal hormone therapy for fracture prevention. *Curr Osteoporos Rep* 2019; **17:** 465–73.
3 Curtis EM, van der Velde R, Moon RJ, et al. Epidemiology of fractures in the United Kingdom 1988–2012: variation with age, sex, geography, ethnicity and socioeconomic status. *Bone* 2016; **87:** 19–26.
4 National Institute for Clinical Excellence. Menopause: identification and management. 2024. https://www.nice.org.uk/guidance/ng23/resources/menopause-identification-and-management-pdf-183733 0217413 (accessed June 18, 2025).
5 Gosset A, Pouillès J-M, Trémollieres F. Menopausal hormone therapy for the management of osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2021; **35:** 101551.
6 Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2022; **328:** 1747–65.
7 Watts NB, Cauley JA, Jackson RD, et al. No increase in fractures after stopping hormone therapy: results from the Women's Health Initiative. *J Clin Endocrinol Metab* 2017; **102:** 302–08.
8 Banks E, Beral V, Reeves G, Balkwill A, Barnes I. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004; **291:** 2212–20.
9 Karim R, Dell RM, Greene DF, Mack WJ, Gallagher JC, Hodis HN. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause* 2011; **18:** 1172–77.
10 Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol* 2004; **103:** 440–46.
11 Vinogradova Y, Dening T, Hippisley-Cox J, Taylor L, Moore M, Coupland C. Use of menopausal hormone therapy and risk of dementia: nested case-control studies using QResearch and CPRD databases. *BMJ* 2021; **374:** n2182.

12 Jick S, Vasilakis-Scaramozza C, Persson R, Neasham D, Kafatos G, Hagberg KW. Use of the CPRD Aurum Database: insights gained from new data quality assessments. *Clin Epidemiol* 2023; **15:** 1219–22.

13 Vinogradova Y, Iyen B, Masud T, Taylor L, Kai J. A protocol to assess risk of fractures associated with use of menopausal hormone therapy: nested case-control study using CPRD. 2024. https://nottingham-repository.worktribe.com/output/34871779/a-protocol-to-assess-risk-of-fractures-associated-with-use-of-menopausal-hormone-therapy-nested-case-control-study-using-cprd (accessed June 16, 2025).

14 Etminan M. Pharmacoepidemiology II: the nested case-control study—a novel approach in pharmacoepidemiologic research. *Pharmacotherapy* 2004; **24:** 1105–09.

15 Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999; **28:** 964–74.

16 Royston P. Multiple imputation of missing values. *Stata J* 2004; **4:** 227–41.

17 Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; **1:** 97–111.

18 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319:** 1492–95.

19 Rikkonen T, Sund R, Sirola J, Honkanen R, Poole KES, Kröger H. Obesity is associated with early hip fracture risk in postmenopausal women: a 25-year follow-up. *Osteoporos Int* 2021; **32:** 769–77.

20 Engel P, Fabre A, Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Risk of osteoporotic fractures after discontinuation of menopausal hormone therapy: results from the E3N cohort. *Am J Epidemiol* 2011; **174:** 12–21.

21 Hundrup YA, Høidrup S, Ekholm O, Davidsen M, Obel EB. Risk of low-energy hip, wrist, and upper arm fractures among current and previous users of hormone replacement therapy: the Danish Nurse Cohort Study. *Eur J Epidemiol* 2004; **19:** 1089–95.

22 Saarelainen J, Hassi S, Honkanen R, et al. Bone loss and wrist fractures after withdrawal of hormone therapy: the 15-year follow-up of the OSTPRE cohort. *Maturitas* 2016; **85:** 49–55.

23 Bagger YZ, Tankó LB, Alexandersen P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004; **34:** 728–35.

24 Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med* 2002; **162:** 665–72.

25 National Institute for Clinical Excellence. Osteoporosis: assessing the risk of fragility fracture. 2017. https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 (accessed June 18, 2025).

26 Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. *Bone* 2017; **105:** 11–17.

27 Lee SJ, Kanis JA. An association between osteoporosis and premenstrual symptoms and postmenopausal symptoms. *Bone Miner* 1994; **24:** 127–34.

28 The North American Menopause Society. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause* 2021; **28:** 973–97.

29 Lambrinoudaki I, Armeni E, Goulis D, et al. Menopause, wellbeing and health: a care pathway from the European Menopause and Andropause Society. *Maturitas* 2022; **163:** 1–14.