Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials
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Authors' objectives
To determine the effect of hormone replacement therapy (HRT) on vertebral fracture rates.

Searching
Recent systematic reviews were used to identify all HRT literature published before 1997. More recent studies (1997 to December 2000) were sought in MEDLINE, EMBASE, the Science Citation Index, and the Cochrane Controlled Trials Register using combinations of the following keywords: 'HRT', 'ERT', 'hormon* replacement', '(o)estrogen replacement', '(o)estradiol', '(o)estrone' and 'dien(o)estrol'. Authors of studies published since 1990, which did not report fracture data as an outcome or adverse event, were contacted to ascertain whether fracture data had been collected. Researchers in the field and pharmaceutical companies were contacted for details of unpublished studies. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of HRT with inactive placebo, calcium with or without vitamin D, or no treatment were eligible if they lasted more than 12 months. The included HRT preparations consisted of oral conjugated oestrogen (0.3 to 0.625 mg), oral oestradiol (1 or 2 mg), and transdermal preparations (50 microg oestradiol or 0.1 mg 17- beta-oestradiol) plus progestin or calcium.

Participants included in the review
The inclusion criteria were not defined in terms of the participants. The women included in the review were: healthy postmenopausal women with low and normal bone mineral density; women with established osteoporosis (including those with vertebral fractures); elderly women and postmenopausal women under 60 years of age; and women with coronary artery disease.

Outcomes assessed in the review
The rates of vertebral fracture were assessed. Fractures were diagnosed radiographically and symptomatically.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Validity was assessed using the 3-item, 5-point scale described by Jadad et al. (see Other Publications of Related Interest). This considers the method of randomisation, concealment allocation, and the reporting of withdrawals and drop-outs. Two reviewers independently assessed validity, and any disagreements were resolved by discussion.

Data extraction
Two reviewers extracted the data independently, and any disagreements were resolved by discussion.
Methods of synthesis
How were the studies combined?
A pooled relative risk (RR) and 95% confidence interval (CI) of fracture were estimated using the random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. Studies recruiting women with and without established osteoporosis, and studies involving older patients (age greater than 60 years) and those with a mean age of less than 60 years, were analysed separately as subgroups.

Results of the review
Thirteen RCTs (6,723 women) were included.

The quality of the trials was generally good. Seven RCTs reported the method of randomisation; 9 RCTs were double-blinded; and almost all trials reported on the drop-outs or withdrawals and gave reasons.

Overall, there was a significant reduction in the risk of fracture among women receiving HRT, compared with those not receiving HRT. The RR was 0.67 (95% CI: 0.45, 0.98, p=0.04).

There was no evidence of statistical heterogeneity (chi-squared 11.94, d.f.=12, p=0.45).

For women with established osteoporosis (3 RCTs), there was a significant reduction in the risk of fracture among women receiving HRT, compared with those not receiving HRT. The RR was 0.47 (95% CI: 0.25, 0.89, p=0.02).

For women without osteoporosis (10 RCTs), there was no significant difference between the treatment groups. The RR was 0.81 (95% CI: 0.50, 1.33, p=0.40).

For studies involving women with a mean age of less than 60 years (5 RCTs), there was no significant difference between the treatment groups in terms of the risk of fracture. The RR was 0.61 (95% CI: 0.16, 2.36).

For women older than 60 years of age, there was a significant reduction in the risk of fracture. The RR was 0.63 (95% CI: 0.41, 0.96).

Authors' conclusions
The use of HRT was associated with a significant reduction in the risk of vertebral fracture, particularly among women with osteoporosis.

CRD commentary
The aims were stated, and the inclusion criteria were defined in terms of the study design, intervention and outcomes. Several relevant sources of literature were searched and attempts were made to locate unpublished material. No language restrictions were applied. The methods used to select the studies were not described. Validity was assessed using validated criteria and details were given of the methods used. Relevant data were tabulated and the methods used to extract the data were described. The data were combined appropriately in a meta-analysis and statistical heterogeneity was assessed. Further analyses were conducted to explore the influence of the participants' age and osteoporotic status on the results, although it is unclear whether these analyses were planned a priori.

The results were clearly reported. The evidence presented supports the authors' conclusions, though the upper 95% CI of the RR of fracture among women receiving HRT compared with no HRT was 0.98 (close to a level indicating no effect).

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors state that ongoing trials are large enough to determine whether HRT does significantly reduce vertebral and other fractures.

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Other publications of related interest

This additional published commentary may also be of interest. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomised trials. JAMA 2001;285:2891-7.

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