Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids

CRD summary
The authors concluded that the relative risk of non-verbral fractures increased by about 12% for each 1,000μg/day increase in dose of inhaled corticosteroids (beclomethasone dipropionate or equivalent) in adults. The reliability of the conclusions is uncertain given a number of weaknesses in the review (potential for publication bias, unclear quality of included studies and small number of included studies).

Authors' objectives
To determine the strength of association between the dose of inhaled corticosteroids and risk of non-vertebral fracture in adults.

Searching
MEDLINE (1950 to 2007) and EMBASE (1988 to 2007) were searched. Search terms were reported. Reference lists of identified relevant studies were handsearched.

Study selection
Case-control studies that assessed the effect of inhaled corticosteroids (with at least two doses reported predominantly as the equivalent dose of beclomethasone dipropionate (BDP) per day) on the risk of non-vertebral fractures were eligible for inclusion. Studies were also eligible for inclusion if they included data on the number of cases and controls using each dose of inhaled corticosteroids and odds ratios (ORs) for the risk of non-vertebral fracture for each inhaled corticosteroids dose compared with no use. Non-adult studies were excluded.

The included studies were conducted in USA, UK and Canada. The studies assessed varied non-vertebral fractures (hip, hip or upper extremity). Mean daily dose of inhaled corticosteroids, BDP or equivalent were varied. Mean age (where reported) ranged from 63 to 81 years. The mean prescription history ranged from one to four years.

Two reviewers assessed studies for inclusion; the authors did not state how any disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data on the slope of coefficients and odds ratios for the risk of non-vertebral fractures, with 95% confidence intervals (CIs), were extracted for each daily dose of inhaled corticosteroids, BDP or equivalent.

The authors did not state how many reviewers conducted data extraction.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using inverse weighting variance meta-analysis. Heterogeneity was assessed using tests of homogeneity and I² tests. Publication bias was assessed using a funnel plot and statistically (details on specific tests were not reported). Sensitivity analysis was performed by examining the association between the risk of non-vertebral fractures and inhaled corticosteroids dose using both random-effects and fixed-effect meta-analyses.

Results of the review
Five matched case-control studies (n=303,719) were included.

Increased doses of inhaled corticosteroids (BDP or equivalent) were associated with an increase in the risk of non-vertebral fracture: fixed-effects OR per 1,000μg increase in daily dose of inhaled corticosteroids (BDP or equivalent)
1.08, 95% CI 1.03 to 1.12, p<0.001 for homogeneity test, I²=78.8%; random-effects OR per 1,000μg increase in daily dose of inhaled corticosteroids (BDP or equivalent) 1.12, 95% CI 1.00 to 1.26, I²=78.8%.

**Authors' conclusions**
The relative risk of non-vertebral fractures increased by about 12% for each 1,000μg/day increase in the dose of inhaled corticosteroids (BDP or equivalent) in older adults.

**CRD commentary**
The review question was clearly stated. Two relevant databases were searched. Publication bias was assessed and no evidence of it was found; however, the possibility of publication bias could not be excluded given the limited attempts to identify unpublished papers and the small number of studies included. Study selection was done in duplicate, which minimised the risk of error and bias; it was unclear whether similar efforts were taken during data extraction. The quality of included studies was unclear since no validity assessment was performed. Appropriate methods were used to combine study results. The authors acknowledged a number of weaknesses in the review (lack of randomised controlled trials, small number of studies, potential confounding).

The reliability of the authors' conclusion is uncertain given a number of weaknesses in the review (potential for publication bias, unclear quality of included studies and small number of included studies).

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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