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Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease

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ABSTRACT

Background

Inhaled corticosteroids form the main therapy for asthma, but there is increasing concern about the potential systematic effects of long-term inhaled corticosteroids including their effect on bone metabolism and bone loss.

Objectives

To determine the effect of inhaled corticosteroids use on biochemical markers of bone turnover, bone mineral density and the development of fractures.

Search methods

We searched the Cochrane Airways Group trials register, electronic reference databases, UK National Research Register, bibliographies of included studies, and contacted pharmaceutical companies.

Selection criteria

Randomised trials of the effect of inhaled steroid versus placebo on markers of bone function and metabolism, in adults with asthma or mild COPD.

Data collection and analysis

Trial quality was assessed and data extracted from the papers included (2 reviewers per paper) and from additional data supplied by the authors.

Main results

Of 438 references found, seven met the inclusion criteria. Three studies were in healthy subjects asthma or COPD. The patients were generally less than 60 years old and the male:female ratio was 2:1. There was no evidence of increased risk of loss of bone mineral density (BMD) or fractures. There was no significant change in osteocalcin at conventional doses of inhaled corticosteroids (Standardised Mean Difference [SMD] -0.34 (95% Confidence Interval [CI] -0.72, 0.04), although a statistically significant change was seen in those studies using experimental doses of inhaled steroid in excess of the doses recommended by the British Thoracic Society SMD 0.97 (95% CI -1.61, -0.34). A

statistically significant change in parathyroid hormone seen in one small short trial (n=10, 6 weeks) may have been due to the trial design and outcome measurements used.

Authors' conclusions

In patients with asthma or mild COPD, there is no evidence of an effect of inhaled corticosteroid at conventional doses given for two or three years on BMD or vertebral fracture. Higher doses were associated with biochemical markers of increased bone turnover, but data on BMD and fractures at these doses are not available. There is a need for further, even longer term prospective studies of conventional and high doses of inhaled corticosteroids.

PLAIN LANGUAGE SUMMARY

Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease

Usual doses of corticosteroids for two or three years for asthma does not weaken bones in younger patients, although long term outcomes and after high doses need more research.

BACKGROUND

Inhaled corticosteroids form the main therapy for asthma, but there is increasing concern about the potential systematic effects of long term inhaled corticosteroids including: bone loss, adrenal suppression, skin thinning, increased cataract formation, decreased linear growth in children, metabolic changes and behavioural abnormalities (Hanania 1995).

There is evidence that inhaled steroids affect bone metabolism (Agertoft 1994), reduces osteocalcin concentrations in health volunteers (Teelucksingh 1991) and reduce lumbar spine density (Anderson 1994). Evidence of the potential risk of bone fractures in patients receiving long-term inhaled steroid therapy (Toogood 1995) could be greater than is suggested by the loss in bone mineral density (Luengo 1991).

Disturbances of bone metabolism are important because of their potential to cause fractures, but fractures are infrequent, requiring extended periods of follow up and long study periods. For this reason biochemical markers of bone metabolism have often been used as surrogate measurements of effects on the bones. Osteoporosis results from an imbalance between bone resorption (measured by, for example, parathyroid hormone and urinary hydroxyproline) and bone formation (measured by, for example, alkaline phosphatase and osteocalcin), with a relative excess of bone resorption causing bone loss in age related osteoporosis. The effect of corticosteroids on bone is primarily to reduce bone formation by a negative effect on osteoblastic function and life span. This is reflected by reductions in markers of bone formation, particularly in osteocalcin concentrations.

Several publications now confirm the validity of biochemical markers in predicting changes in bone turnover (Garnero 1998, Miller 1999). The bone turnover value of biochemical markers partly reflects the strong correlation with bone mineral density but evidence also exists for an effect independent and additive to bone density measurements. The best validated biochemical markers of bone formation include serum alkaline phosphatase (both total and bone specific), osteocalcin and carboxyterminal propeptide of type 1 procollagen (PICP). Whilst the best validated resorption markers encompass urinary pyridinoline cross links of type I collagen, hydroxyproline, C-terminal and N-terminal telopeptides of collagen. Although anti resorptive therapy reduces bone turnover, at present it is not certain whether biochemical markers are clinically useful for individual patients (Riggs 2000).

This review was planned as a review of inhaled corticosteroids in asthma supported by data from studies in healthy people. Since then, three large 3-year studies of inhaled corticosteroids in COPD have been published. In one of these (EUROSCOP 1999), the patients had mild disease (FEV1 73% predicted) and were quite young (mean 52 years). The patients in the other two (Burge 2000b, Wise 2000b) were older (mean 56-65 years) and with more severe airways obstruction (FEV1 50 - 65% predicted). For this review, we have included just EUROSCOP 1999, the other trials will be considered in a revised version of this review.

OBJECTIVES

To determine whether use of inhaled corticosteroids has a harmful effect on bone, in terms of development of fractures, a reduction in bone mineral density (BMD), or changes in specified biochemical markers.
A secondary objective was to explore the potential for biochemical markers to predict patients at increased risk of osteoporosis and fractures.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials

Types of participants

Adults with or without a clinical diagnosis of asthma or chronic obstructive pulmonary disease (COPD).

Types of interventions

Randomisation to an inhaled corticosteroid or matching placebo.

Types of outcome measures

Osteoporosis as suggested by:

Bone fracture (by type)
Bone Mineral Density
Bone Metabolism measures:
total alkaline phosphatase
bone-specific alkaline phosphatase
serum osteocalcin
amino terminal propeptide of type I procollagen (PINP)
carboxyterminal propeptide of type 1 procollagen (PICP)
urinary hydroxyproline/creatinine
urinary calcium:creatine ratio
urinary galactosyl hydroxylysine
pyridinium (cross-links)
pyridinoline (PYD)
deoxypyridinoline (DPD)
N-terminal cross-linked telopeptide (NTX)
C-terminal cross-linked telopeptide (CTX)
type I collagen C-telopeptide (ICTP)
tartrate resistant acid phosphatase (TRAP)
plasma parathyroid hormone

Search methods for identification of studies

An advanced search was carried out on the following databases: MEDLINE, EMBASE, CINAHL, SCIENCE CITATION INDEX (BIDS ISI) and the COCHRANE TRIALS REGISTER (CCTR).

The studies were identified using the following search strategy:

1. STEROID$.tw.
2. CORTICOSTEROID$.tw.
3. CORTICO-STEROID$.tw.
4. (BECLOMETHASONE or BECONASE or BECLOVENT or VANCENASE or VANCERIL OR AEROBEC or BECLAZONE or BECOTIDE or BECLOFORTE or BUDESONIDE or PULMICORT or RHINOCORT or FLUTICASONE or FLOVENT or FLONASE or CUTIVATE or FLIXOTIDE or FLIXONASWE or QVAR or ZONIVENT or FILAIR OR ASMABEC or BECODISK$).tw.
5. 1OR 2 OR 3 OR 4
6. INHAL$.tw.

7. 5 AND 6
8. (OSTEO$ or BONE$ or FRACTURE$ or BMD or CALCITONIN or CREATININE or CREATINE or CALCIUM or OSTEOCALCIN or HYDROXYPROLINE or PYRIDINIUM or PYRIDINOLINE or DEOXYPYRIDINOLINE or TELOPEPTIDE or (PROPEPTIDE$ OF TYPE I PROCOLLAGEN) OR (ALKALINE PHOSPHATASE) or (ACID PHOSPHATASE) or (GALACTOSYL HYDROXYLYSINE) OR (PARATHYROID HORMONE$)).tw.
9. 7 AND 8
10. LIMIT TO HUMAN

ALL TIME PERIODS UP To 1st November 1999 CONSIDERED initially. The search was updated in July 2001.
ALL COUNTRIES AND LANGUAGES CONSIDERED.

Other potential studies were identified by:

- Checking the bibliographies of the included studies
- Searching key journals (electronically, and by hand)
- Contacting key authors to locate other suitable data (unpublished or ongoing)
- Contacting pharmaceutical companies (3M, Medeva, AstraZeneca, GlaxoWelcome) for RCT's (unpublished or ongoing)

Data collection and analysis

Data were extracted from the selected studies and entered into Review Manager. Trials were combined using the Review Manager software. For continuous variables, the results of the individual studies were calculated as fixed effects weighted mean difference (WMD) or standardised mean difference (SMD) and a 95% confidence interval (CI) was calculated for each study. The impact of different dosing regimes was assessed using subgroup analysis. Where two outcomes have been assessed in different units (e.g. nmol/L and mcg/L) these were combined using a SMD. For dichotomous variables (bone fractures), a random effects odds ratio (OR) with 95% confidence intervals (95% CI) was calculated for individual studies. Sub-group analyses was planned categorising the participants into healthy subjects or those with asthma or chronic obstructive pulmonary disease. An additional analysis was planned when the primary trial data showed that some studies had used doses of inhaled corticosteroids above the currently recommended dosing regimes. These doses were termed 'conventional' and 'experimental'.

We were examining inhaled steroids for a harmful rather than a treatment effect. Falls in alkaline phosphatase and osteocalcin were harmful, as were rises in PTH or urinary hydroxyproline.

RESULTS

Description of studies

The search of the Cochrane database provided 226 abstracts, and a further 189 came from running the search in MEDLINE CINAHL, EMBASE and BIDS ISI, giving a total of 415 references, which reduced to 288 on removal of duplicates. Two reviewers independently ascertained the relevance of each title and abstract (MB, KH, AJ, GR). Five relevant abstracts were found in the National Research Register and details of 18 studies were obtained from the pharmaceutical companies. From all of these, 18 full papers were considered in detail, each by 2 reviewers (MB, JF, KH, AJ, MS) and where there was discrepancy between reviewers, this was adjudicated at a team meeting. Seven studies were included in the final analysis. Contact was successfully made with the authors of all except Li 1999 (despite two mailings to the first author, and e-mail correspondence to the second author), and AstraZeneca were able to provide additional data on the EUROSCOP study. The search was updated in July 2001, leading to the inclusion of the Tattersfield 2001study.

Seven studies met the inclusion criteria. Four (EUROSCOP 1999; Kerstjens 1994; Li 1999; Tattersfield 2001) recruited subjects with "mild" asthma or chronic obstructive pulmonary disease (total 1256 men and 614 women), and three (Hodsman 1991; Leech 1993; Toogood 1991) recruited healthy volunteers (total 41 men and 78 women), although in one of these (Leech 1993), 4 out of 21 subjects had mild asthma. Duration of follow-up varied from 9 weeks to 3 years. In Hodsman 1991, Toogood 1991 and Leech 1993, follow-up was up to 12 weeks, and the other studies, 104 weeks or more. In both Hodsman 1991 and Toogood 1991, data were extracted from the first half of the studies, in which inhaled steroid was compared with placebo.

The numbers of participants in the trials ranged from 21 to 1277, with a total of 1989 in the seven studies. EUROSCOP 1999 was the largest trial, and also had the highest average age (52 years); the other 6 studies all had average ages of 40 or below. One study recruited smokers (EUROSCOP 1999), one reported 20% of participants smoked (Tattersfield 2001), two recruited non-smokers, and in 3 smoking status was not stated.

Only EUROSCOP 1999 and Tattersfield 2001 formally looked for bone fractures as an outcome measure. Li 1999, Tattersfield 2001and EUROSCOP 1999 considered bone mineral density. Data from Hodsman 1991, Toogood 1991 and Leech 1993 has been included for osteocalcin. Li 1999 reported that "Mean serum osteocalcin . . . did not differ significantly at any time point", but the actual figures were not reported, and we were unable to make contact with the first or second authors. Tattersfield 2001 also reported osteocalcin and urinary pyridinoline, but as % change from baseline of geometric mean values of the area under the curve. There was a significant change ($p<0.05$) in serum osteocalcin in the beclomethasone group, but not budesonide group, compared with the reference group. Kerstjens 1994 reported on procollagen type 1 carboxy terminal propeptide (PICP). Data from Hodsman 1991 on alkaline phosphatase, parathyroid hormone, and urinary hydroxyproline is included.

Beclomethasone, budesonide and fluticasone were the inhaled steroids used. "Conventional doses" were interpreted as those up to the maximum dose of beclomethasone or budesonide (22000 mmcg daily, or fluticasone (11000 mmcg daily recommended in the British Thoracic Society Asthma Guidelines (BTS 1997). Both Hodsman 1991 (budesonide 3.2 mg daily) and Toogood 1991 (budesonide 22.4 mmg daily used doses in excess of this in one arm of their studies, and these are referred to in the comparisons as "experimental dose".

A wide variety of outcome measures were reported; where these corresponded with the outcome measures detailed in our protocol, the figures were included for the meta-analysis (except where raw data could not be obtained to facilitate this process).

Effect modifiers are detailed in the table of Characteristics of Included Studies and include the list below. We have included subgroup analyses of; conventional maintenance dose vs high dose inhaled steroids; trials in asthma or COPD patients vs those in healthy volunteers, and those where duration of treatment was greater or less than 3 months.
Asthma therapy (exposure to inhaled steroids)
Strength of inhaled steroid drug(s) taken
Duration of treatment
Age
Lifestyle data - e.g. height, weight, BMI, smoking, alcohol, exercise
Other asthma medication - e.g. oral steroids and bronchodilators
Non-asthma medication - e.g. HRT, calcium, Vitamin D
Compliance
Delivery system (e.g. clickhaler, turbohaler, spacer device)
Duration of follow-up

In terms of one important risk factor (age), the mean age of the study populations was quite low , in the range 20 - 60 years, with a mean age of 30-40 in most studies, but in EUROSCOP 1999 the mean age was 52 years. Sex is another important risk factor, summing the number of patients across the studies, the male:female ratio was 2:1.

Risk of bias in included studies

KH and JF independently assessed the methodological quality of the included RCTs using the Cochrane approach to quality assessment of allocation concealment. Trials were scored using the following principles:

Grade A: Adequate concealment.
Grade B: Uncertain concealment.
Grade C: Clearly Inadequate concealment.

Each study was also assessed for validity on a 0 - 5 scale described by Jadad as follows:

1. Was the study described as randomised ? (1 = yes; 0 = no).
2. Was the study described as double-blind? (1 = yes; 0= no).
3. Was there a description of withdrawals and drop-out? (1 = yes; 0 = no)
4. Was the method of randomisation well described and appropriate? (1 = yes; 0 = no)
5. Was the method of double-blinding well described and appropriate? (1 = yes; 0 = no)
6. Deduct 1 point if methods for randomisation or blinding were inappropriate.

Effects of interventions

Using the Cochrane concealment allocation criteria, there was on A grade trial (Hodsman 1991), four Grade B (EUROSCOP 1999, Kerstjens 1994, Li 1999, Toogood 1991) and two Grade C (Leech 1993, Tattersfield 2001). There was agreement between the two reviewers on all studies. Using the Jadad criteria, three studies were graded 3 - 5 (EUROSCOP 1999, Hodsman 1991, Li 1999) and four were graded 0 - 2 (Kerstjens 1994, Leech 1993, Tattersfield 2001, Toogood 1991). The reviewers disagreed over one paper only, and then by 1 only point.

BONE FRACTURES
The two studies that collected fracture data prospectively (EUROSCOP 1999, Tattersfield 2001) showed no significant effect of inhaled steroids on vertebral fractures at conventional therapeutic doses (Peto OR 1.87, 95% CI 0.5, 7.03).

BONE MINERAL DENSITY
The pooled results from three studies (EUROSCOP 1999, Li 1999, Tattersfield 2001) showed no significant effect of inhaled steroids in patients with asthma or COPD on bone mineral density measured by Dual Energy Xray Absorptiometry (DEXA) at lumber spine WMD 0.01(95%CI -0.08, 0.10), or femoral neck, (EUROSCOP 1999, Tattersfield 2001) WMD 0.61 (95% CI -0.34, 1.56).

BIOCHEMICAL MARKERS

1. Osteocalcin
Overall, with all data at all doses of inhaled corticosteroids combined in meta-analyses, there is no significant effect on osteocalcin SMD -0.34 (95%CI -0.72, 0.04). Li 1999 also considered osteocalcin after two years, but we were unable to obtain details of their results, the paper only reporting a graph. Indications from the graph would give an approximate effect size of -0.025, i.e. small effect favouring treatment. When considering the arms of those studies that used 'experimental' doses of inhaled corticosteroid (i.e. those in excess of those recommended in the BTS guidelines), there was a statistically significant lowering (i.e. worsening of osteocalcin SMD 0.97 (95%CI -1.61, -0.34).

2. Other biochemical markers
A statistically significant fall (iDixie in parathyroid hormone WMD -10.0 (95%CI -17.7, -2.3) in favour of the treatment group, and alkaline phosphatase WMD -13.0 (95%CI -24.0, -2.0) in favour of the control group, was seen at conventional dosing only, in the Hodsman 1991 study, but this may be spurious for reasons explored below. The differences did not reach significance when the higher dosage regimens were included. There were no statistically significant results included from among the studies looking at patients with a history of asthma or COPD. These were also the papers with the longer follow-up. No significant effect was shown on urinary hydroxyproline (p=0.7, WMD -0.08, 95%CI -0.5, 0.36) or C-terminal propeptide of type one procollagen WMD 11.6, 95%CI -3.1, 26.3).

DISCUSSION

This review has systematically evaluated seven papers which met our entry criteria aimed at determining whether inhaled corticosteroids have a harmful effect on bone in terms of fractures, bone mineral density or specific biochemical markers of bone turnover. At conventional doses of inhaled steroid there appears to be no significant effect on bone metabolism as measured by osteocalcin, bone mineral density, or clinical fracture rate. The effect on alkaline phosphatase and parathyroid hormone seen at conventional doses was not seen at the higher doses. The data for both sets of results comes from the very small study of Hodsman 1991. The alkaline phosphatase analyses is reported to have been "standard" suggesting that it was not bone specific, so would have varied with changes in serum alkaline phosphatase from muscular and hepatic sources, as well as bone. Hodsman 1991 has explained the parathyroid hormone result (which suggested that treatment with conventional doses of inhaled steroid was better than placebo) by pointing out that the recruits were placed on a calcium restricted diet for the study, and that this may have given rise to the slight rise in PTH seen in the control group.

Comparison of serum osteocalcin measured by different immunoassay kits is difficult in the absence of an internationally agreed standard (Swaminathan 1997). Additionally, samples should be collected on ice, stored at -70 degrees, and thawed only once. The effect of prolonged freezing on degradation and reliability is unclear. The studies included here used a variety of collecting and storage regimens.

The evidence available for this review suggest that inhaled steroids in currently recommended doses incur little risk of osteoporosis and fractures over the medium term (months to a few years), however there are important qualifications attached to this conclusion. First, asthma is life-long so the period of these studies is small compared to the potential period of exposure to inhaled corticosteroids. Second, the studies have been carried out in relatively low-risk patients (mainly under the age of 60 years and predominantly males). In the 3-year studies in moderate-severe COPD patients not yet included in this review (Burge 2000b, Wise 2000b), no increase in the risk of bone fractures was reported in either trial, although there was a small fall in bone mineral density in Wise 2000b after three years, but not before.

The available trials provided no opportunity to assess the role of routine monitoring of biochemical markers of the bone turnover to identify patients potentially at greater risk of inhaled steroid-induced fractures or osteoporosis.

AUTHORS' CONCLUSIONS

Implications for practice

Treatment with inhaled corticosteroids at conventional doses over two or three years has not shown a significant effect on bone mineral density or increased risk of fracture in younger patients with asthma or mild COPD (i.e. at lower risk of osteoporosis and fractures). At present, current evidence also does not support the use of biochemical markers in the clinical setting.

Implications for research

There is a need for further long term studies on both conventional and experimental doses of inhaled steroid, using fractures, bone mineral density and biochemical markers as outcomes. Such studies would ideally be prospective but could be supported by retrospective case control and cohort studies, looking particularly for fractures, comparing different steroids in different dosages. The role of biochemical markers in determining bone turnover in the clinical setting is at present uncertain. Our evidence suggests further research in this area may provide useful information in evaluating clinical outcomes and response to therapy. In studies using biochemical markers, careful attention needs to be paid to confounding factors (such as diet or time of specimen collection) and technical details (such as assay used, and specimen storage temperature) when planning further research in this area.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

EUROSCOP 1999

Methods	randomised, double blind duration: 3 years follow-up: 71%
Participants	"mild COPD patients who continue to smoke" male / female: 932 / 345

EUROSCOP 1999 *(Continued)*

	Av age: 52.4yr +/- 7.7 (placebo) 52.5 +/- 7.5 (budesonide)
Interventions	budesonide 400mcg or placebo twice daily.
Outcomes	after 104 weeks: vertebral fracture; bone mineral density (BMD); adverse effects; spirometry;
Notes	Jadad score 3. smoking education and inhaler compliance prior to randomisation. BMD data to be published soon.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hodsman 1991

Methods	"random allocation" double blind double dummy Duration: 6 weeks Follow up: 100%
Participants	healthy subjects male / female: 17 / 33 Av Age: 33, SD 9 Smoking status not stated.
Interventions	5 groups, each n=10; oral prednisolone 10mg or 40mg daily; inhaled budesonide 3.2mg or 0.8mg daily; or placebo; ethics committee stipulation that participants to be on a calcium restricted diet.
Outcomes	measured at 1 week; serum osteocalcin; calcium, phosphate, creatinine, alk.phos.,24hr urinary Ca, Pi & creatinine; i-PTH; 1,25-(OH)2D3; cortisol; urinary hydroxyproline; urinary cAMP;
Notes	Jadad score 4. pill counting + inhaler weights to assess compliance. Authors provided raw data from the end of week one before cross-over for inclusion in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kerstjens 1994

Methods	double blind Duration: 2.5 yrs (retrospective) Follow-up: 100%
Participants	"airways obstruction" male / female: 101 / 54 Av Age: 40.0, SD 12

Kerstjens 1994 *(Continued)*

	Smoking status not stated.
Interventions	terbutaline 200mcg plus either beclomethasone 200mcg qds, n = 70, or ipratropium bromide 160mcg od, n = 44, or placebo, n = 41 (placebo & ipratropium pooled for analysis)
Outcomes	PICP, ICTP;
Notes	Jadad score 2. No measure of compliance. No samples taken within 1 month of oral steroids. Authors provided raw data, including separate figures for ipratropium group, and for placebo (pooled in original paper). From phase 2 of a study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Leech 1993

Methods	randomised crossover. Unmarked inhalers not identical. duration: 9 weeks Follow up: 100%
Participants	healthy non-smoker volunteers (4 mild asthma) 21 women Age: 21 - 41
Interventions	3 cycles of 2 weeks inhaler use then 1 week no inhaler. 1st week of each cycle 2 puffs bd; 2nd week 4 puffs bd; inhalers were placebo or budesonide 200mcg/puff, or beclomethasone 250mcg/puff.
Outcomes	serum osteocalcin;
Notes	Jadad score 2. All original raw data destroyed in a flood. Therefore unable to take pre-cross over data for the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Li 1999

Methods	randomised, double blind duration: 104 weeks Follow-up: 66% fluticasone, 53% placebo
Participants	"mild persistent asthma"

Li 1999 *(Continued)*

	male / female: 55 / 9 Av Age: 29.55, range 18-49. Smoking status not stated.
Interventions	fluticasone 500mcg or placebo twice daily.
Outcomes	bone mineral density; serum osteocalcin; HPA-axis function evaluations; urinary N-telopeptide; ophthalmic exams.
Notes	Jadad score 3. Less than 1 years total ever oral steroid use, + no oral steroids in month prior to recruitment; up to 2 x 10 day courses oral steroid use allowed during trial. Raw data for osteocalcin not obtained from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tattersfield 2001

Methods	randomised, open study. Duration 2 years. follow-up 64%
Participants	"mild asthma" (FEV1 86% predicted) male / female 168 / 206 Age 20 - 60, Av 35 years Smokers 20%
Interventions	beclomethasone 500mcg daily(rising to 2000mcg if required), budesonide 400mcg daily (rising to 1600mcg daily if required) or non-corticosteroid asthma treatment alone.
Outcomes	Fracture, bone mineral density; serum osteocalcin; urinary pyridinoline; urinary deoxypyridinoline
Notes	Jadad score 2. Results presented on those completing follow-up, rather than intention to treat, although it was commented that analysis on basis of intention to treat would not make significant difference to results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Toogood 1991

Methods	placebo controlled, double blind, cross-over. duration: 4 weeks 1st intervention, 2 wks wash out, 4 wks 2nd intervention. follow-up: 100%
Participants	healthy, non-smoking adults male / female: 24 / 24

Toogood 1991 *(Continued)*

	Av age: 32.1, SD 8.8
Interventions	budesonide 1.2mg (n=20) or 2.4mg (n=20) or placebo(n=8)
Outcomes	serum osteocalcin; 24hr urinary free cortisol; plasma cortisol; urinary calcium; urinary hydroxyproline; urinary phosphate; candida counts.
Notes	Jadad score 2. further sub-group analysis comparing 8am/8pm dosing with 8am/noon. Authors provided detailed raw data. Baseline data only available for ur. hydroxyproline placebo group, so not included in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barnes 1996	trial abandoned as it was impossible to find enough patients in general practice in the UK with mild asthma who had not already been started on inhaled steroids.
Bootsma 1996	cross-over trial comparing two different steroids, with placebo in the run-in and wash-out periods only
Clark 1997	different outcome measures - plasma cortisol
Dempsey 1999	different outcome measures (urinary cortisol:creatinine ratios)
Egan 1999	randomisation to different inhaled steroid products, no placebo inhaler
Gross 1999	compared inhaled steroid and placebo in their effect on the RECOVERY of osteocalcin levels after suppression by oral steroids
Harmanci 1998	Comparison between two steroids, no placebo group
Herrala 1994	No randomisation to a placebo group
Hughes 1999	Two steroids; no placebo
Johnell 1999	inhaled steroids compared with a reference group given theophylline, nedocromil and ipratropium, the effect of which on bone metabolism is not known
Kos-Kudla 1997	used oral steroid
Malo 1999	Comparison of two steroids; no placebo group
Nikolaizik 1996	different outcome measures - cortisol and adreno-corticotrophic hormone
Padfield 1993	Not a RCT

Study	Reason for exclusion
Paggiaro 1998	used cortisol as the out come measure
Pauwels 1998	comparison between two steroids; no placebo group
Struijs 1997	COPD patients who needed steroids were randomised to beclomethasone or budesonide. Patients not requiring corticosteroids were the comparison group. BMD, alkaline phosphatase, osteocalcin, PICP and ICTP were measured.
Suissa 2000	Cohort study looking at inhaled steroid use and death rates.
Toogood 1988	Not an RCT
Vickers 1999	trial discontinued at the end of the feasibility phase because of the difficulties with recruitment - the majority of patients were given steroids at time of diagnosis of asthma, making it difficult to re-cruit for randomisation.
Wilson 1997	different outcomes - plasma cortisol and urinary cortisol and creatinine excretion
Wilson 1997b	different outcome measures - creatinine excretion
Wilson 1998	randomisation to budesonide (via turbohaler) OR triamcinolone (via integrated actuator/spacer), but not to a placebo group
Wilson 1998c	randomisation to oral prednisolone OR nebulised budesonide no placebo group
Wilson 1999	different outcomes - plasma cortisol and urinary cortisol/creatinine excretion
Wilson1998b	different outcomes - plasma cortisol and urinary cortisol creatinine ratios
Wood 1999	no randomisation to placebo

DATA AND ANALYSES

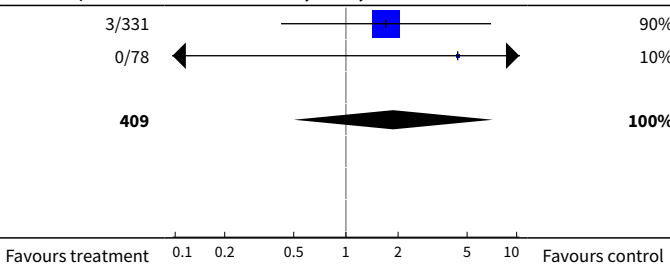
Comparison 1. inhaled steroid vs placebo - all outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 vertebral fractures	2	892	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.50, 7.03]
2 Osteocalcin	3	141	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.72, 0.04]
2.1 Parallel studies	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.28, -0.18]
2.2 Cross-over study	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.51, 0.54]
3 Bone mineral density	3	792	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Change at lumbar spine (% fall)	3	419	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
3.2 Change at femoral neck (% fall)	2	373	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.34, 1.56]
4 alkaline phosphatase IU/L	1	30	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-25.30, 3.30]
5 Parathyroid hormone (ng/l)	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-15.73, 0.73]
6 urinary hydroxyproline (umol/L GF)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.52, 0.36]
7 PICP mcg/L	1	105	Mean Difference (IV, Fixed, 95% CI)	11.57 [-3.11, 26.25]

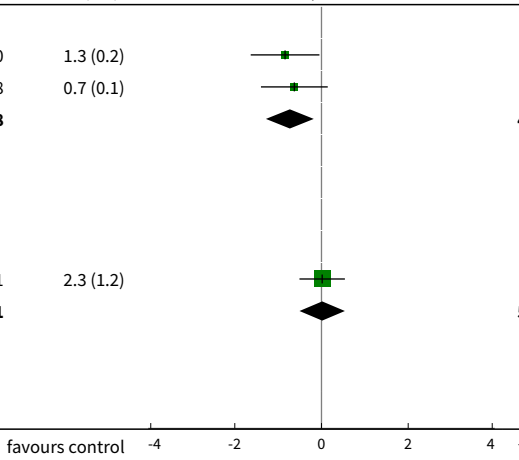
Analysis 1.1. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 1 vertebral fractures.

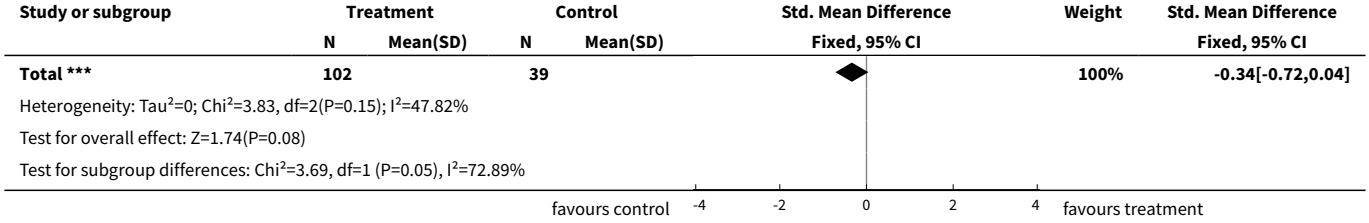
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EUROSCOP 1999	5/322	3/331		90%	1.7[0.42,6.87]
Tattersfield 2001	1/161	0/78		10%	4.41[0.07,288.46]
Total (95% CI)	**483**	**409**		**100%**	**1.87[0.5,7.03]**
Total events: 6 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					



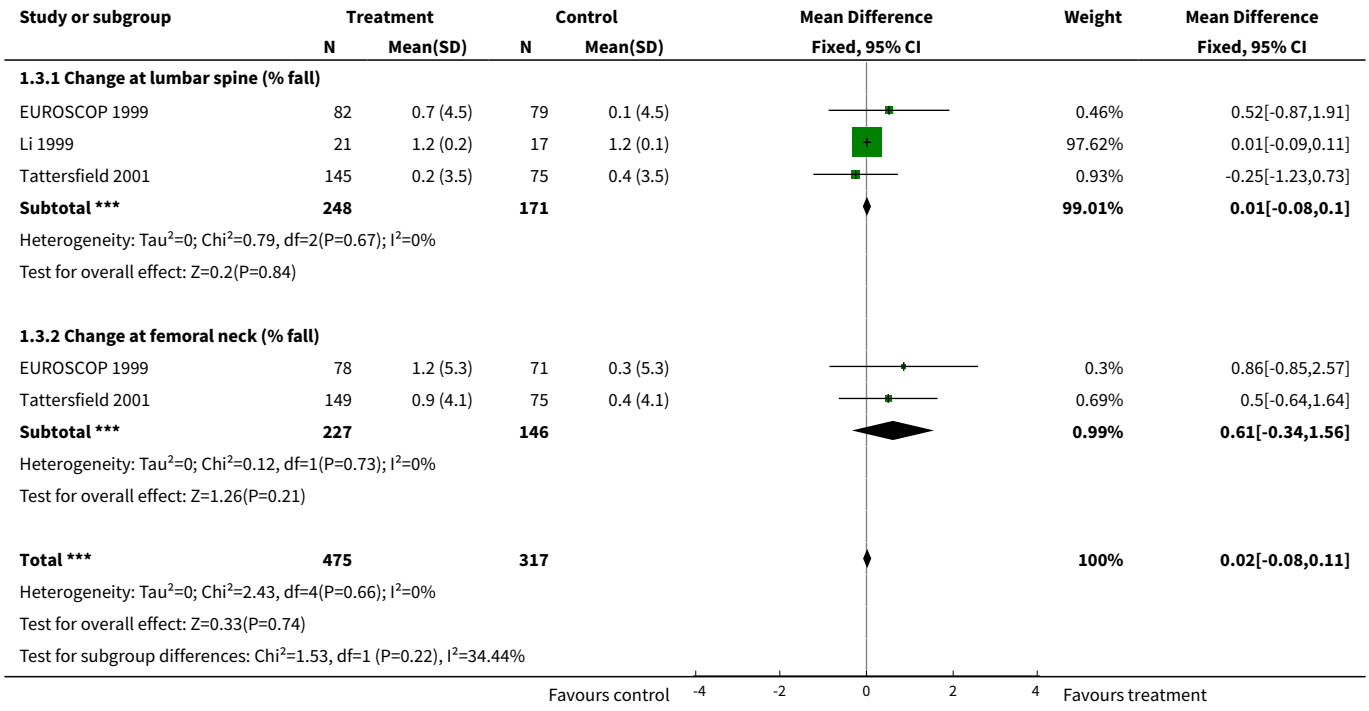
Analysis 1.2. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 2 Osteocalcin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.2.1 Parallel studies							
Hodsman 1991	20	0.8 (0.6)	10	1.3 (0.2)		23%	-0.84[-1.63,-0.05]
Toogood 1991	40	0.5 (0.3)	8	0.7 (0.1)		24.35%	-0.63[-1.4,0.14]
Subtotal ***	**60**		**18**			**47.35%**	**-0.73[-1.28,-0.18]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=2.59(P=0.01)							
1.2.2 Cross-over study							
Leech 1993	42	2.3 (1.3)	21	2.3 (1.2)		52.65%	0.02[-0.51,0.54]
Subtotal ***	**42**		**21**			**52.65%**	**0.02[-0.51,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							

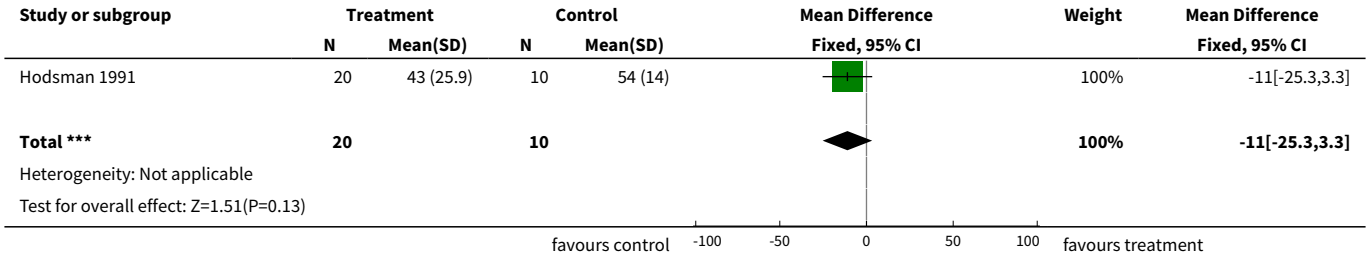




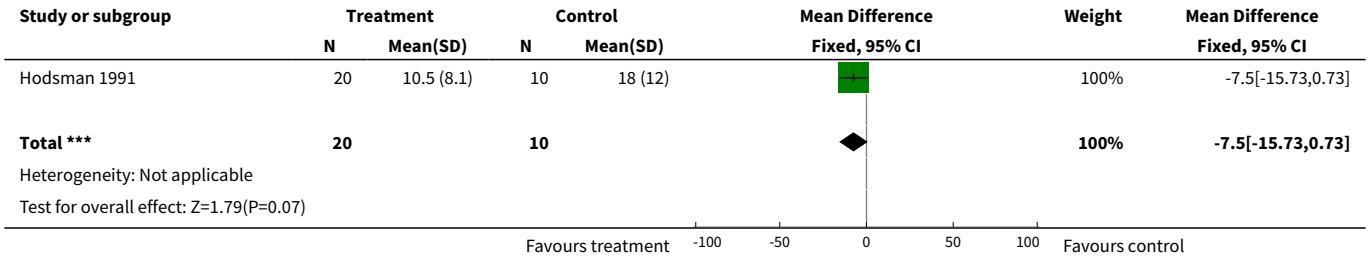
Analysis 1.3. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 3 Bone mineral density.



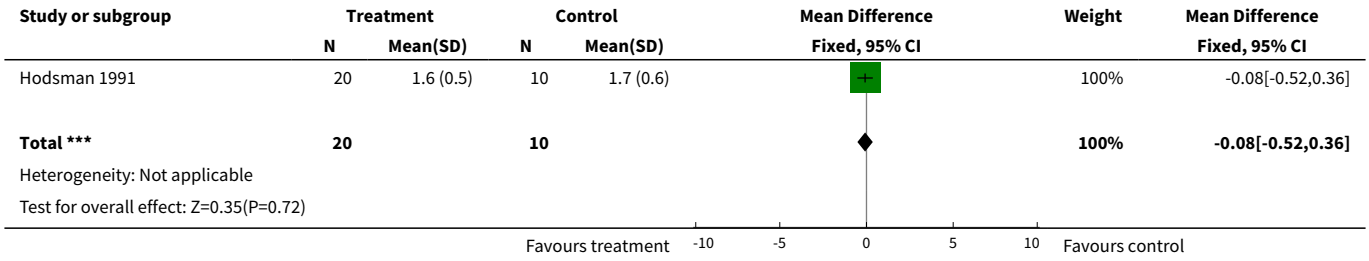
Analysis 1.4. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 4 alkaline phosphatase IU/L.



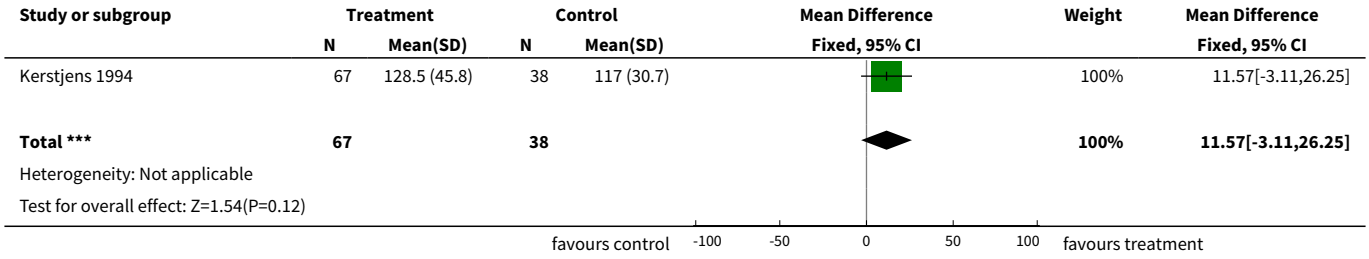
Analysis 1.5. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 5 Parathyroid hormone (ng/l).



Analysis 1.6. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 6 urinary hydroxyproline (umol/L GF).



Analysis 1.7. Comparison 1 inhaled steroid vs placebo - all outcomes, Outcome 7 PICP mcg/L.



Comparison 2. inhaled steroid vs placebo - Jadad scores 0-2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin	2	111	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.62, 0.25]
1.1 Parallel study	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-0.63 [-1.40, 0.14]
1.2 Cross-over study	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.51, 0.54]
2 PICP mcg/L	1	105	Mean Difference (IV, Fixed, 95% CI)	11.57 [-3.11, 26.25]
3 Vertebral fracture	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.41 [0.07, 288.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Bone Mineral Density	1	444	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.67, 0.81]
4.1 lumber spine (% fall)	1	220	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.23, 0.73]
4.2 neck of femur (% fall)	1	224	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.64, 1.64]

Analysis 2.1. Comparison 2 inhaled steroid vs placebo - Jadad scores 0-2, Outcome 1 Osteocalcin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.1.1 Parallel study							
Toogood 1991	40	0.5 (0.3)	8	0.7 (0.1)		31.62%	-0.63[-1.4,0.14]
Subtotal ***	**40**		**8**			**31.62%**	**-0.63[-1.4,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.59(P=0.11)							
2.1.2 Cross-over study							
Leech 1993	42	2.3 (1.3)	21	2.3 (1.2)		68.38%	0.02[-0.51,0.54]
Subtotal ***	**42**		**21**			**68.38%**	**0.02[-0.51,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Total ***	**82**		**29**			**100%**	**-0.19[-0.62,0.25]**
Heterogeneity: Tau^2=0; Chi^2=1.82, df=1(P=0.18); I^2=45.19%							
Test for overall effect: Z=0.85(P=0.4)							
Test for subgroup differences: Chi^2=1.82, df=1 (P=0.18), I^2=45.19%							

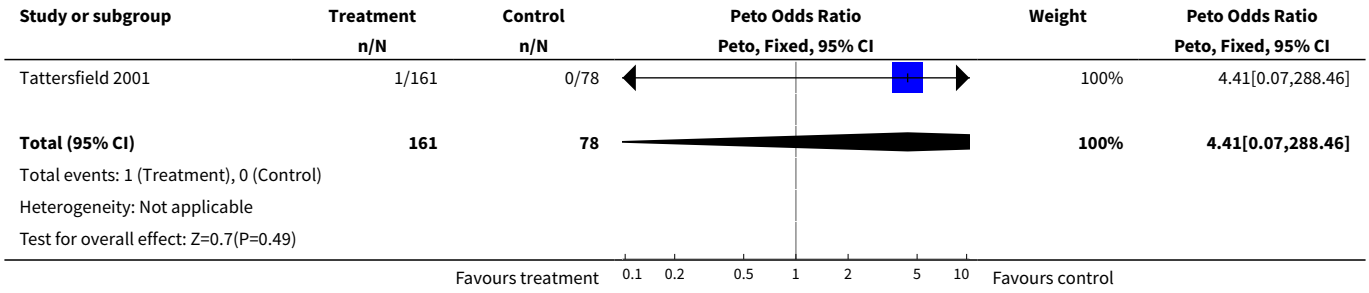
favours control — favours treatment

Analysis 2.2. Comparison 2 inhaled steroid vs placebo - Jadad scores 0-2, Outcome 2 PICP mcg/L.

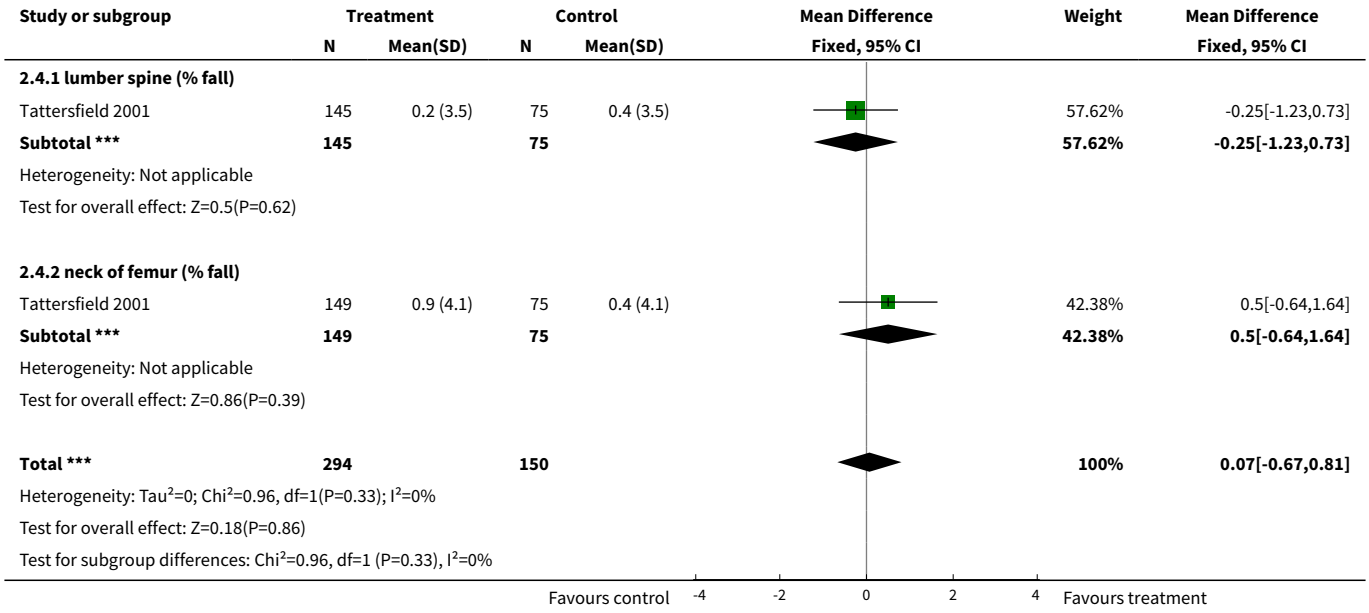
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kerstjens 1994	67	128.5 (45.8)	38	117 (30.7)		100%	11.57[-3.11,26.25]
Total ***	**67**		**38**			**100%**	**11.57[-3.11,26.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							

Favours control — Favours treatment

Analysis 2.3. Comparison 2 inhaled steroid vs placebo - Jadad scores 0-2, Outcome 3 Vertebral fracture.



Analysis 2.4. Comparison 2 inhaled steroid vs placebo - Jadad scores 0-2, Outcome 4 Bone Mineral Density.



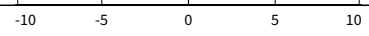
Comparison 3. inhaled steroid vs placebo Jadad scores 3-5

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 osteocalcin	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.85, -0.03]
2 urinary hydroxyproline (umol/L GF)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.52, 0.36]
3 parathyroid hormone ng/L	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-15.73, 0.73]
4 alkaline phosphatase	1	30	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-25.30, 3.30]
5 Bone mineral density	2	348	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.21, 0.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Change at femoral neck (% fall)	1	149	Mean Difference (IV, Fixed, 95% CI)	0.86 [-0.85, 2.57]
5.2 Change at lumbar spine (% fall)	2	199	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.24, 0.29]
6 Vertebral fracture	1	653	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.70 [0.42, 6.87]

Analysis 3.1. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 1 osteocalcin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	20	0.8 (0.6)	10	1.3 (0.5)		100%	-0.44[-0.85,-0.03]
Total ***	**20**		**10**			**100%**	**-0.44[-0.85,-0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.04)							



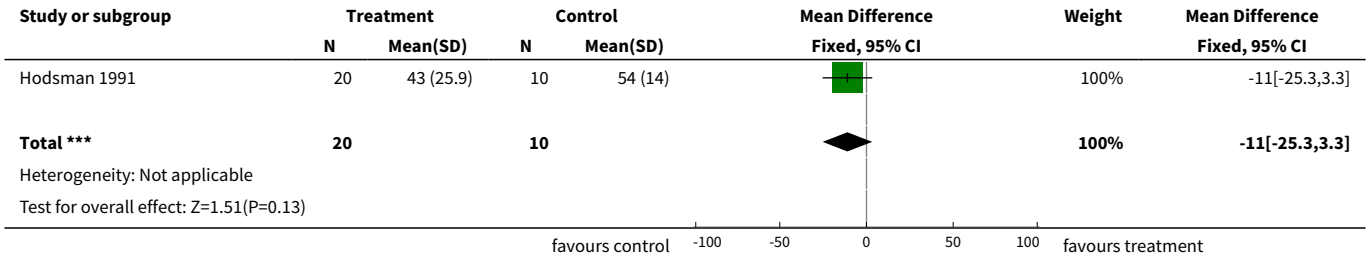
Analysis 3.2. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 2 urinary hydroxyproline (umol/L GF).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	20	1.6 (0.5)	10	1.7 (0.6)		100%	-0.08[-0.52,0.36]
Total ***	**20**		**10**			**100%**	**-0.08[-0.52,0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.72)							

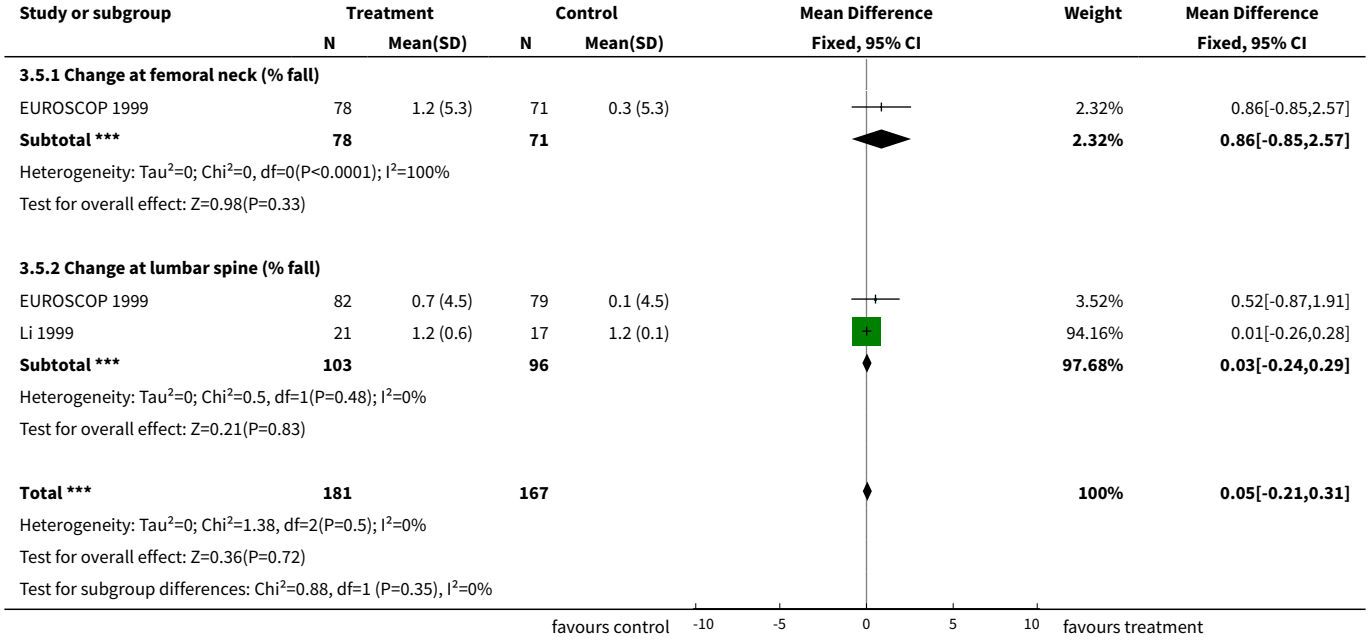
Analysis 3.3. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 3 parathyroid hormone ng/L.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	20	10.5 (8.1)	10	18 (12)		100%	-7.5[-15.73,0.73]
Total ***	**20**		**10**			**100%**	**-7.5[-15.73,0.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.79(P=0.07)							

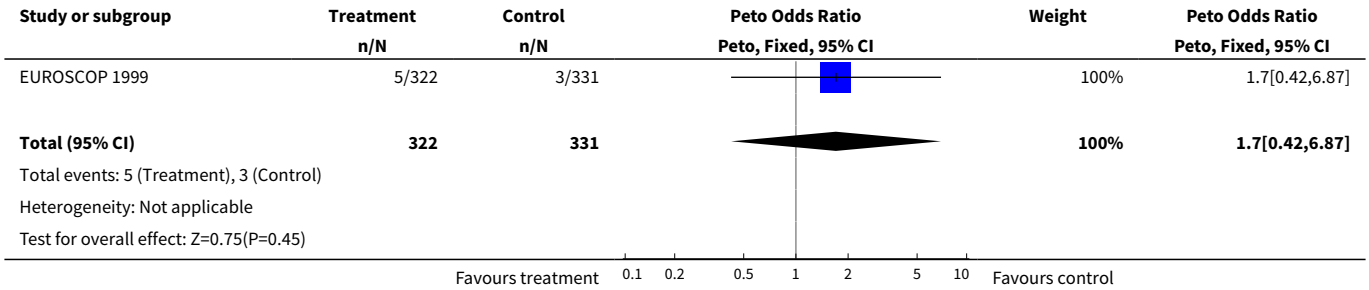
Analysis 3.4. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 4 alkaline phosphatase.



Analysis 3.5. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 5 Bone mineral density.



Analysis 3.6. Comparison 3 inhaled steroid vs placebo Jadad scores 3-5, Outcome 6 Vertebral fracture.

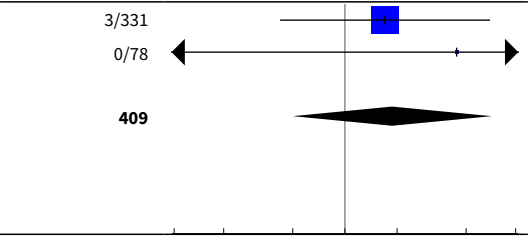


Comparison 4. inhaled steroid vs placebo - Conventional therapeutic dose of steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vertebral fracture	2	892	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.50, 7.03]
2 Bone mineral density	3	792	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]
2.1 Change at lumbar spine (% fall)	3	419	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
2.2 Change at femoral neck (% fall)	2	373	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.34, 1.56]
3 PICP mcg/L	1	105	Mean Difference (IV, Fixed, 95% CI)	11.57 [-3.11, 26.25]
4 Alkaline phosphatase IU/L	1	20	Mean Difference (IV, Fixed, 95% CI)	-13.0 [-24.04, -1.96]
5 Parathyroid hormone ng/L	1	20	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-17.67, -2.33]
6 urinary hydroxyproline	1	20	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.48, 0.56]
7 Osteocalcin	3	111	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.58, 0.21]
7.1 Parallel studies	2	48	Std. Mean Difference (IV, Fixed, 95% CI)	-0.45 [-1.06, 0.16]
7.2 Cross-over study	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.51, 0.54]

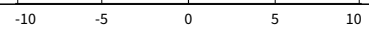
Analysis 4.1. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 1 Vertebral fracture.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EUROSCOP 1999	5/322	3/331		90%	1.7[0.42,6.87]
Tattersfield 2001	1/161	0/78		10%	4.41[0.07,288.46]
Total (95% CI)	**483**	**409**		**100%**	**1.87[0.5,7.03]**
Total events: 6 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					



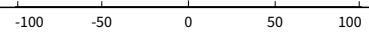
Analysis 4.2. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 2 Bone mineral density.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.2.1 Change at lumbar spine (% fall)							
EUROSCOP 1999	82	0.7 (4.5)	79	0.1 (4.5)		0.46%	0.52[-0.87,1.91]
Li 1999	21	1.2 (0.2)	17	1.2 (0.1)		97.62%	0.01[-0.09,0.11]
Tattersfield 2001	145	0.2 (3.5)	75	0.4 (3.5)		0.93%	-0.25[-1.23,0.73]
Subtotal ***	**248**		**171**			**99.01%**	**0.01[-0.08,0.1]**
Heterogeneity: Tau^2=0; Chi^2=0.79, df=2(P=0.67); I^2=0%							
Test for overall effect: Z=0.2(P=0.84)							
4.2.2 Change at femoral neck (% fall)							
EUROSCOP 1999	78	1.2 (5.3)	71	0.3 (5.3)		0.3%	0.86[-0.85,2.57]
Tattersfield 2001	149	0.9 (4.1)	75	0.4 (4.1)		0.69%	0.5[-0.64,1.64]
Subtotal ***	**227**		**146**			**0.99%**	**0.61[-0.34,1.56]**
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%							
Test for overall effect: Z=1.26(P=0.21)							
Total ***	**475**		**317**			**100%**	**0.02[-0.08,0.11]**
Heterogeneity: Tau^2=0; Chi^2=2.43, df=4(P=0.66); I^2=0%							
Test for overall effect: Z=0.33(P=0.74)							
Test for subgroup differences: Chi^2=1.53, df=1 (P=0.22), I^2=34.44%							



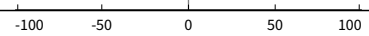
Analysis 4.3. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 3 PICP mcg/L.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kerstjens 1994	67	128.5 (45.8)	38	117 (30.7)		100%	11.57[-3.11,26.25]
Total ***	**67**		**38**			**100%**	**11.57[-3.11,26.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							



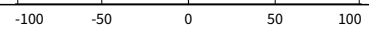
Analysis 4.4. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 4 Alkaline phosphatase IU/L.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	10	41 (11)	10	54 (14)		100%	-13[-24.04,-1.96]
Total ***	**10**		**10**			**100%**	**-13[-24.04,-1.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.31(P=0.02)							



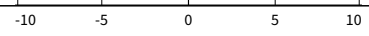
Analysis 4.5. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 5 Parathyroid hormone ng/L.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	10	8 (3)	10	18 (12)		100%	-10[-17.67,-2.33]
Total ***	**10**		**10**			**100%**	**-10[-17.67,-2.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.56(P=0.01)							



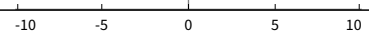
Analysis 4.6. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 6 urinary hydroxyproline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	10	1.7 (0.6)	10	1.7 (0.6)		100%	0.04[-0.48,0.56]
Total ***	**10**		**10**			**100%**	**0.04[-0.48,0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.15(P=0.88)							



Analysis 4.7. Comparison 4 inhaled steroid vs placebo - Conventional therapeutic dose of steroid, Outcome 7 Osteocalcin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
4.7.1 Parallel studies							
Hodsman 1991	10	1 (0.7)	10	1.3 (0.5)		19.94%	-0.41[-1.3,0.48]
Toogood 1991	20	0.6 (0.3)	8	0.7 (0.1)		22.76%	-0.48[-1.32,0.35]
Subtotal ***	**30**		**18**			**42.69%**	**-0.45[-1.06,0.16]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%							
Test for overall effect: Z=1.46(P=0.15)							
4.7.2 Cross-over study							
Leech 1993	42	2.3 (1.3)	21	2.3 (1.2)		57.31%	0.02[-0.51,0.54]
Subtotal ***	**42**		**21**			**57.31%**	**0.02[-0.51,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Total ***	**72**		**39**			**100%**	**-0.18[-0.58,0.21]**
Heterogeneity: Tau^2=0; Chi^2=1.32, df=2(P=0.52); I^2=0%							
Test for overall effect: Z=0.91(P=0.36)							
Test for subgroup differences: Chi^2=1.3, df=1 (P=0.25), I^2=23.32%							



Comparison 5. inhaled steroid vs placebo - experimental dose of steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin - parallel studies	2	48	Std. Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.61, -0.34]
2 Alkaline phosphatase	1	20	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-32.36, 14.36]
3 Parathyroid hormone	1	20	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-15.09, 5.09]
4 Urinary hydroxyproline	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.65, 0.25]

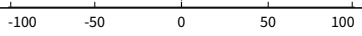
Analysis 5.1. Comparison 5 inhaled steroid vs placebo - experimental dose of steroid, Outcome 1 Osteocalcin - parallel studies.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Hodsman 1991	10	0.6 (0.6)	10	1.3 (0.5)		44.07%	-1.14[-2.1,-0.18]
Toogood 1991	20	0.5 (0.2)	8	0.7 (0.1)		55.93%	-0.84[-1.69,0.01]
Total ***	**30**		**18**			**100%**	**-0.97[-1.61,-0.34]**
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.64); I^2=0%							
Test for overall effect: Z=2.99(P=0)							

Favours control — Favours treatment

Analysis 5.2. Comparison 5 inhaled steroid vs placebo - experimental dose of steroid, Outcome 2 Alkaline phosphatase.

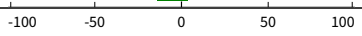
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	10	45 (35)	10	54 (14)		100%	-9[-32.36,14.36]
Total ***	**10**		**10**			**100%**	**-9[-32.36,14.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.75(P=0.45)							



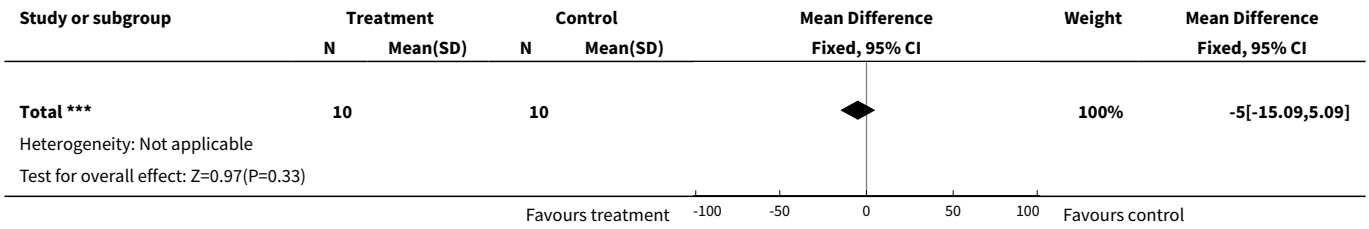
Favours control — Favours treatment

Analysis 5.3. Comparison 5 inhaled steroid vs placebo - experimental dose of steroid, Outcome 3 Parathyroid hormone.

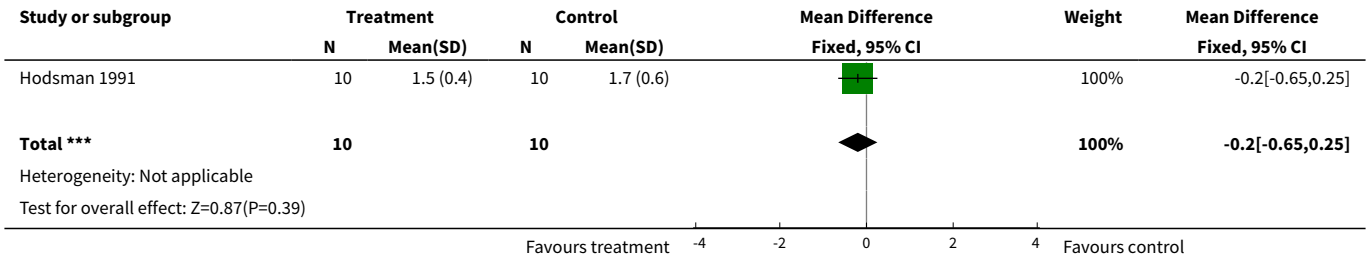
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	10	13 (11)	10	18 (12)		100%	-5[-15.09,5.09]



Favours treatment — Favours control



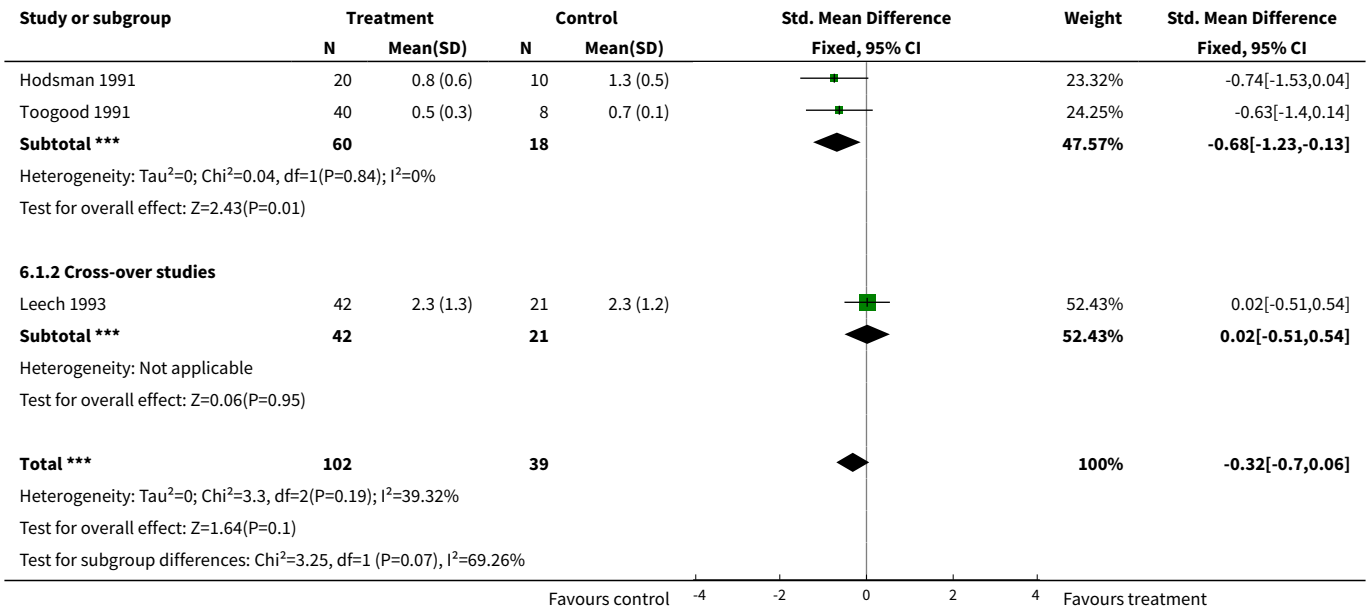
Analysis 5.4. Comparison 5 inhaled steroid vs placebo - experimental dose of steroid, Outcome 4 Urinary hydroxyproline.



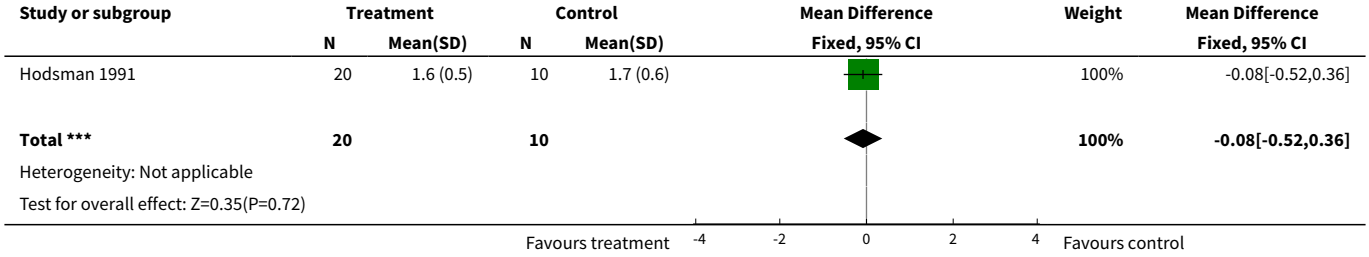
Comparison 6. inhaled steroid vs placebo - healthy recruits

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin	3	141	Std. Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.70, 0.06]
1.1 Parallel studies	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.68 [-1.23, -0.13]
1.2 Cross-over studies	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.51, 0.54]
2 Urinary hydroxyproline (umol/L GF)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.52, 0.36]
3 Parathyroid hormone (ng/L)	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-15.73, 0.73]
4 Alkaline phosphatase	1	30	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-25.30, 3.30]

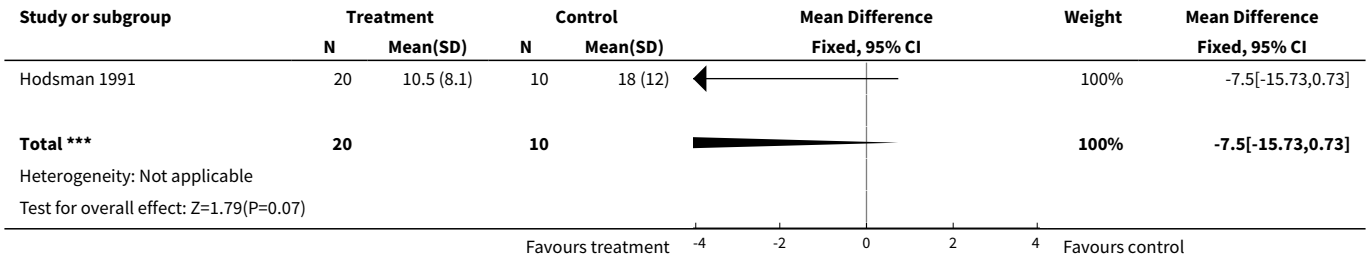
Analysis 6.1. Comparison 6 inhaled steroid vs placebo - healthy recruits, Outcome 1 Osteocalcin.



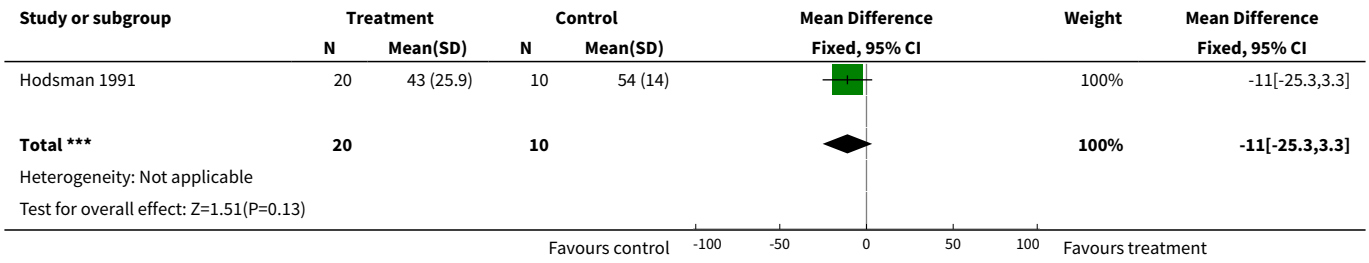
Analysis 6.2. Comparison 6 inhaled steroid vs placebo - healthy recruits, Outcome 2 Urinary hydroxyproline (umol/L GF).



Analysis 6.3. Comparison 6 inhaled steroid vs placebo - healthy recruits, Outcome 3 Parathyroid hormone (ng/L).



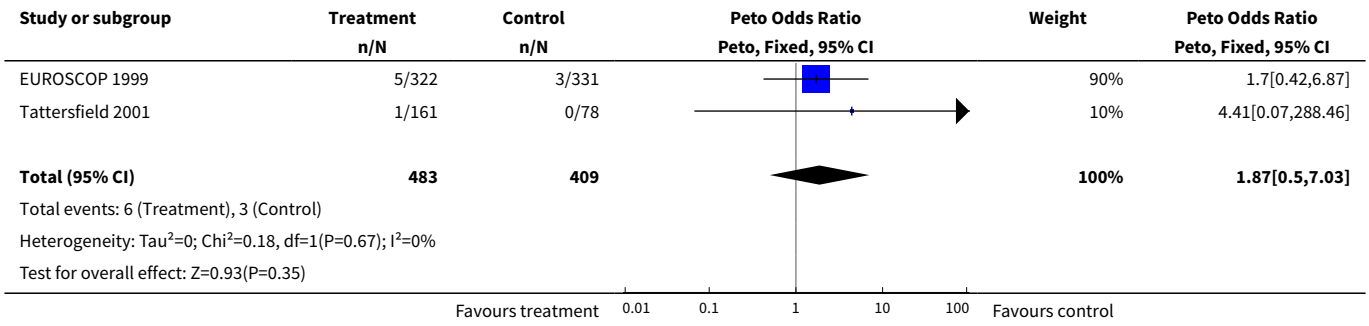
Analysis 6.4. Comparison 6 inhaled steroid vs placebo - healthy recruits, Outcome 4 Alkaline phosphatase.



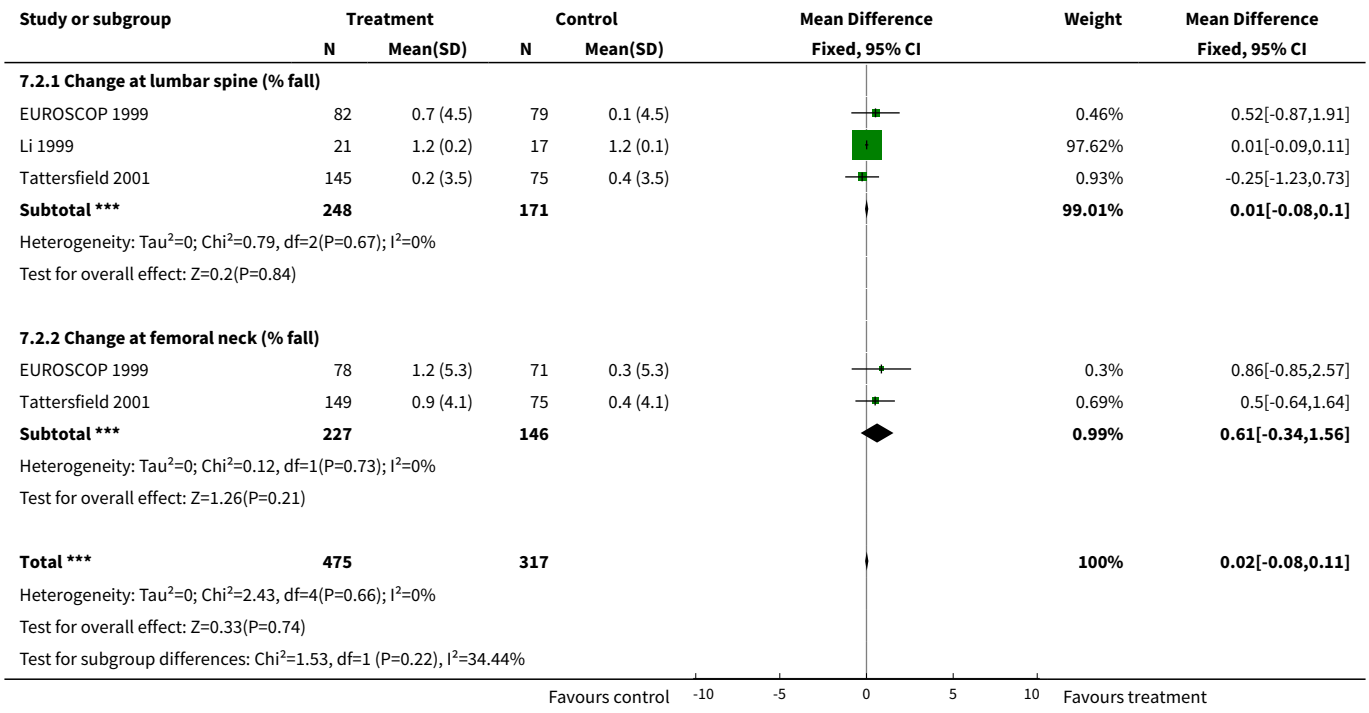
Comparison 7. inhaled steroid vs placebo - asthmatic or COPD recruits

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vertebral fracture	2	892	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.50, 7.03]
2 Bone MIneral Density	3	792	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]
2.1 Change at lumbar spine (% fall)	3	419	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
2.2 Change at femoral neck (% fall)	2	373	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.34, 1.56]
3 PICP (mcg/L)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 inhaled steroid vs placebo - asthmatic or COPD recruits, Outcome 1 Vertebral fracture.



Analysis 7.2. Comparison 7 inhaled steroid vs placebo - asthmatic or COPD recruits, Outcome 2 Bone MIneral Density.



Comparison 8. inhaled steroid vs placebo - treatment & follow-up </= 12 weeks

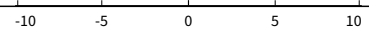
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin	3	141	Std. Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.70, 0.06]
1.1 Parallel studies	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.68 [-1.23, -0.13]
1.2 Cross-over studies	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.51, 0.54]
2 urinary hydroxyproline umol/L GF	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.52, 0.36]
3 Parathyroid ng/L	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-15.73, 0.73]
4 Alkaline Phosphatase IU/L	1	30	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-25.30, 3.30]

Analysis 8.1. Comparison 8 inhaled steroid vs placebo - treatment & follow-up </= 12 weeks, Outcome 1 Osteocalcin.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.1.1 Parallel studies							
Hodsman 1991	20	0.8 (0.6)	10	1.3 (0.5)		23.32%	-0.74[-1.53,0.04]
Toogood 1991	40	0.5 (0.3)	8	0.7 (0.1)		24.25%	-0.63[-1.4,0.14]
Subtotal ***	**60**		**18**			**47.57%**	**-0.68[-1.23,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%							
Test for overall effect: Z=2.43(P=0.01)							
8.1.2 Cross-over studies							
Leech 1993	42	2.3 (1.3)	21	2.3 (1.2)		52.43%	0.02[-0.51,0.54]
Subtotal ***	**42**		**21**			**52.43%**	**0.02[-0.51,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Total ***	**102**		**39**			**100%**	**-0.32[-0.7,0.06]**
Heterogeneity: Tau^2=0; Chi^2=3.3, df=2(P=0.19); I^2=39.32%							
Test for overall effect: Z=1.64(P=0.1)							
Test for subgroup differences: Chi^2=3.25, df=1 (P=0.07), I^2=69.26%							

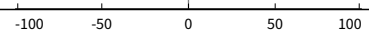
Analysis 8.2. Comparison 8 inhaled steroid vs placebo - treatment & follow-up </= 12 weeks, Outcome 2 urinary hydroxyproline umol/L GF.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	20	1.6 (0.5)	10	1.7 (0.6)		100%	-0.08[-0.52,0.36]
Total ***	**20**		**10**			**100%**	**-0.08[-0.52,0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.72)							

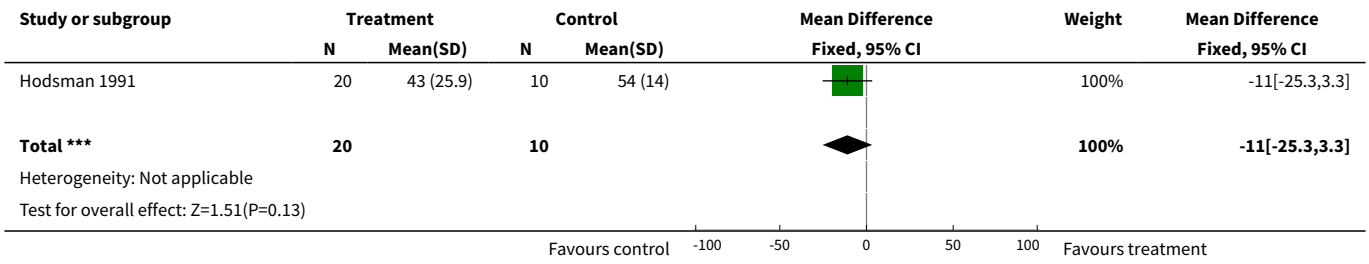


Analysis 8.3. Comparison 8 inhaled steroid vs placebo - treatment & follow-up </= 12 weeks, Outcome 3 Parathyroid ng/L.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hodsman 1991	20	10.5 (8.1)	10	18 (12)		100%	-7.5[-15.73,0.73]
Total ***	**20**		**10**			**100%**	**-7.5[-15.73,0.73]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.79(P=0.07)							



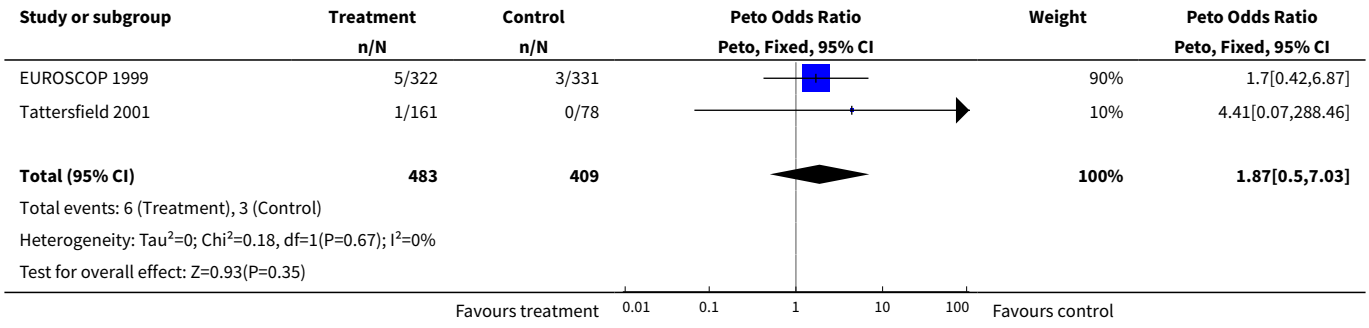
Analysis 8.4. Comparison 8 inhaled steroid vs placebo - treatment & follow-up </= 12 weeks, Outcome 4 Alkaline Phosphatase IU/L.



Comparison 9. inhaled steroid vs placebo - treatment & follow-up > 12 weeks

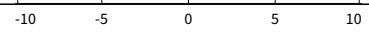
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vertebral fractures	2	892	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.50, 7.03]
2 Bone mineral density	3	792	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]
2.1 Change at femoral neck (% fall)	2	373	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.34, 1.56]
2.2 Change at lumber spine (% fall)	3	419	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.10]
3 PICP mcg/l	1	105	Mean Difference (IV, Fixed, 95% CI)	11.57 [-3.11, 26.25]

Analysis 9.1. Comparison 9 inhaled steroid vs placebo - treatment & follow-up > 12 weeks, Outcome 1 Vertebral fractures.



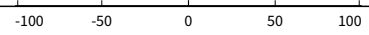
Analysis 9.2. Comparison 9 inhaled steroid vs placebo - treatment & follow-up > 12 weeks, Outcome 2 Bone mineral density.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.2.1 Change at femoral neck (% fall)							
EUROSCOP 1999	78	1.2 (5.3)	71	0.3 (5.3)		0.3%	0.86[-0.85,2.57]
Tattersfield 2001	149	0.9 (4.1)	75	0.4 (4.1)		0.69%	0.5[-0.64,1.64]
Subtotal ***	**227**		**146**			**0.99%**	**0.61[-0.34,1.56]**
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%							
Test for overall effect: Z=1.26(P=0.21)							
9.2.2 Change at lumber spine (% fall)							
EUROSCOP 1999	82	0.7 (4.5)	79	0.1 (4.5)		0.46%	0.52[-0.87,1.91]
Li 1999	21	1.2 (0.2)	17	1.2 (0.1)		97.62%	0.01[-0.09,0.11]
Tattersfield 2001	145	0.2 (3.5)	75	0.4 (3.5)		0.93%	-0.25[-1.23,0.73]
Subtotal ***	**248**		**171**			**99.01%**	**0.01[-0.08,0.1]**
Heterogeneity: Tau^2=0; Chi^2=0.79, df=2(P=0.67); I^2=0%							
Test for overall effect: Z=0.2(P=0.84)							
Total ***	**475**		**317**			**100%**	**0.02[-0.08,0.11]**
Heterogeneity: Tau^2=0; Chi^2=2.43, df=4(P=0.66); I^2=0%							
Test for overall effect: Z=0.33(P=0.74)							
Test for subgroup differences: Chi^2=1.53, df=1 (P=0.22), I^2=34.44%							



Analysis 9.3. Comparison 9 inhaled steroid vs placebo - treatment & follow-up > 12 weeks, Outcome 3 PICP mcg/l.

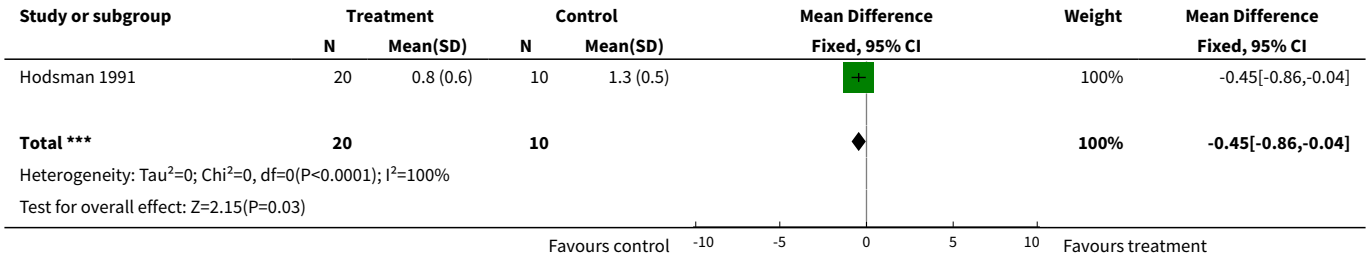
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kerstjens 1994	67	128.5 (45.8)	38	117 (30.7)		100%	11.57[-3.11,26.25]
Total ***	**67**		**38**			**100%**	**11.57[-3.11,26.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							



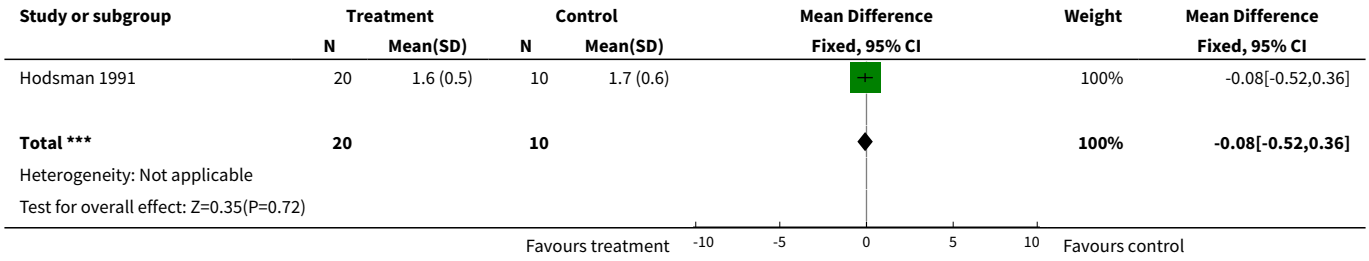
Comparison 10. inhaled steroid vs placebo - Cochrane Concealment A

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin mcg/l	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.86, -0.04]
2 urinary hydroxyproline (umol/L GF)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.52, 0.36]
3 Parathyroid hormone ng/l	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.5 [-15.73, 0.73]
4 Alkaline phosphatase IU/L	1	30	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-25.30, 3.30]

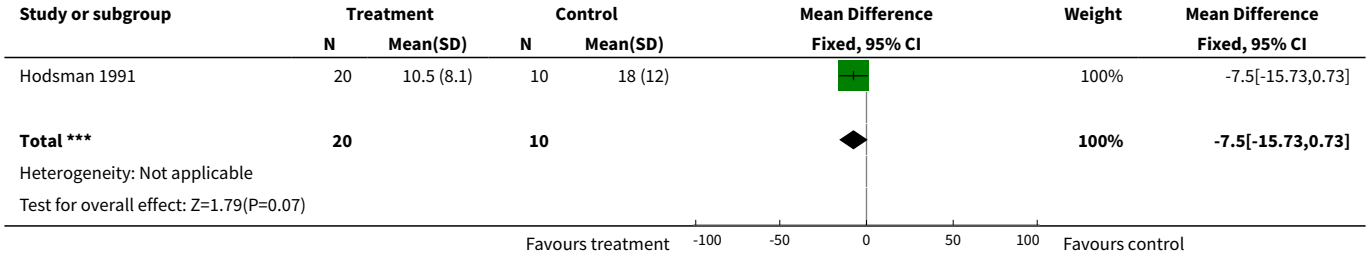
Analysis 10.1. Comparison 10 inhaled steroid vs placebo - Cochrane Concealment A, Outcome 1 Osteocalcin mcg/l.



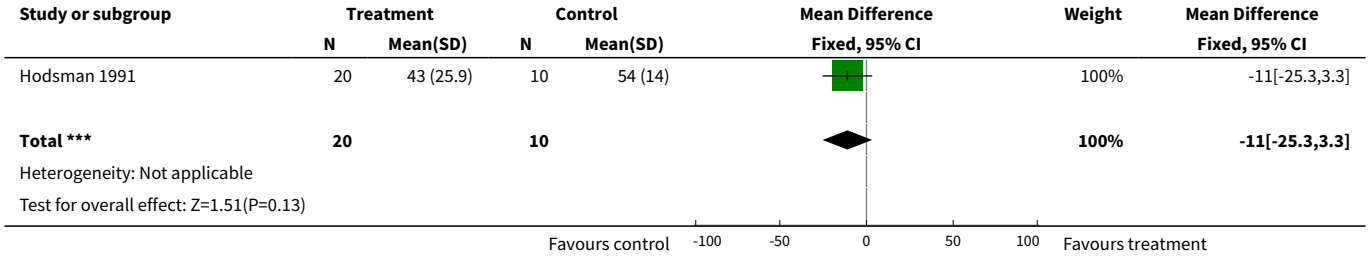
Analysis 10.2. Comparison 10 inhaled steroid vs placebo - Cochrane Concealment A, Outcome 2 urinary hydroxyproline (umol/L GF).



Analysis 10.3. Comparison 10 inhaled steroid vs placebo - Cochrane Concealment A, Outcome 3 Parathyroid hormone ng/l.



Analysis 10.4. Comparison 10 inhaled steroid vs placebo - Cochrane Concealment A, Outcome 4 Alkaline phosphatase IU/L.

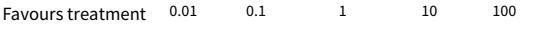


Comparison 11. inhaled steroid vs placebo - Cochrane Concealment B

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vertebral fractures	1	653	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.70 [0.42, 6.87]
2 Bone mineral density	2	348	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.21, 0.31]
2.1 Change at femoral neck (% fall)	1	149	Mean Difference (IV, Fixed, 95% CI)	0.86 [-0.85, 2.57]
2.2 Change at lumbar spine (% fall)	2	199	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.24, 0.29]
3 PICP mcg/L	1	105	Mean Difference (IV, Fixed, 95% CI)	11.57 [-3.11, 26.25]
4 Osteocalcin nmol/l	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.27, -0.03]

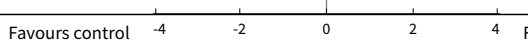
Analysis 11.1. Comparison 11 inhaled steroid vs placebo - Cochrane Concealment B, Outcome 1 Vertebral fractures.

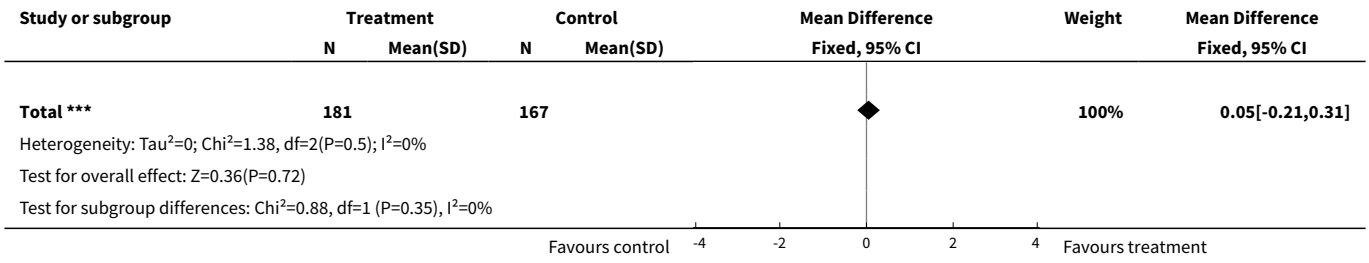
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EUROSCOP 1999	5/322	3/331		100%	1.7[0.42,6.87]
Total (95% CI)	**322**	**331**		**100%**	**1.7[0.42,6.87]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					



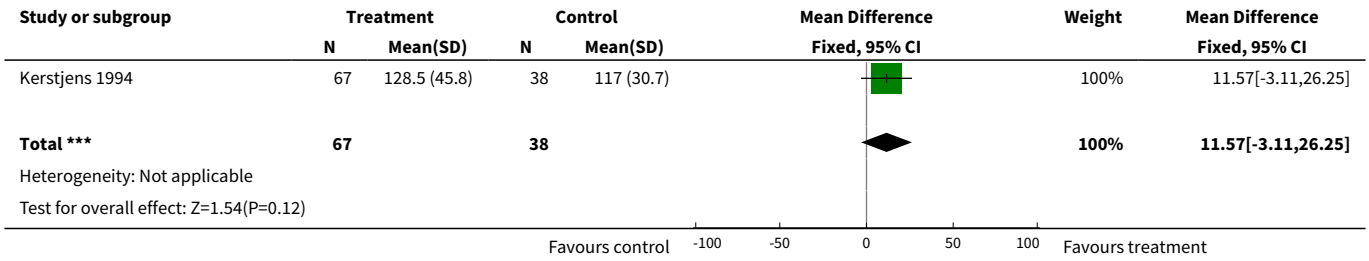
Analysis 11.2. Comparison 11 inhaled steroid vs placebo - Cochrane Concealment B, Outcome 2 Bone mineral density.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.2.1 Change at femoral neck (% fall)							
EUROSCOP 1999	78	1.2 (5.3)	71	0.3 (5.3)		2.32%	0.86[-0.85,2.57]
Subtotal ***	**78**		**71**			**2.32%**	**0.86[-0.85,2.57]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.98(P=0.33)							
11.2.2 Change at lumbar spine (% fall)							
EUROSCOP 1999	82	0.7 (4.5)	79	0.1 (4.5)		3.52%	0.52[-0.87,1.91]
Li 1999	21	1.2 (0.6)	17	1.2 (0.1)		94.16%	0.01[-0.26,0.28]
Subtotal ***	**103**		**96**			**97.68%**	**0.03[-0.24,0.29]**
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%							
Test for overall effect: Z=0.21(P=0.83)							

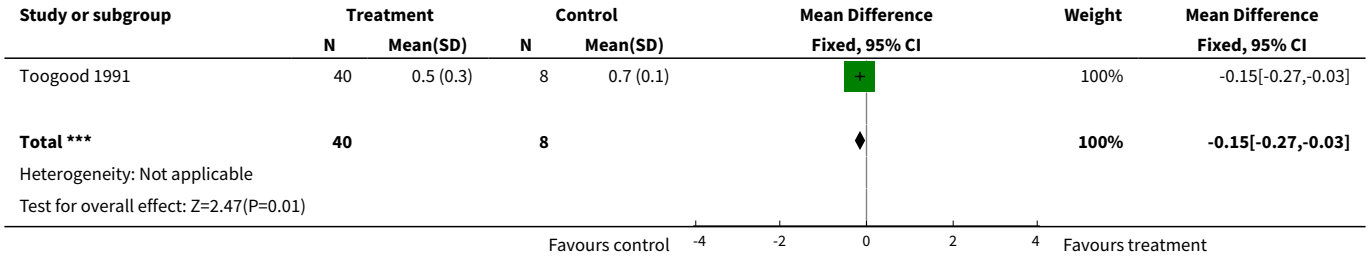




Analysis 11.3. Comparison 11 inhaled steroid vs placebo - Cochrane Concealment B, Outcome 3 PICP mcg/L.



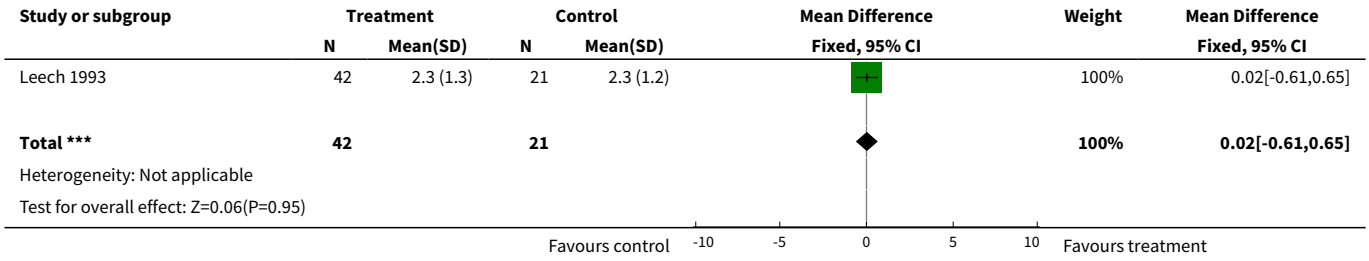
Analysis 11.4. Comparison 11 inhaled steroid vs placebo - Cochrane Concealment B, Outcome 4 Osteocalcin nmol/l.



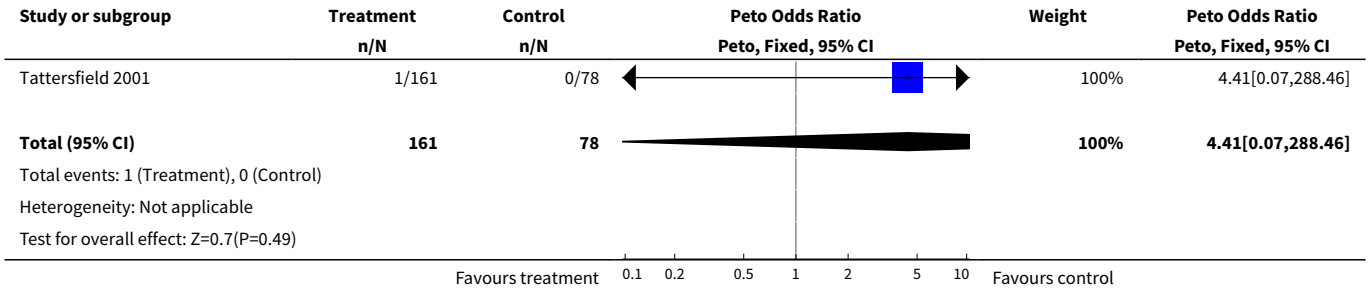
Comparison 12. inhaled steroid vs placebo - Cochrane Concealment C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteocalcin mcg/l, cross-over	1	63	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.61, 0.65]
2 Vertebral fracture	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.41 [0.07, 288.46]
3 Bone mineral density	1	444	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.67, 0.81]
3.1 lumbar spine (% fall)	1	220	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.23, 0.73]
3.2 Neck of femur (% fall)	1	224	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.64, 1.64]

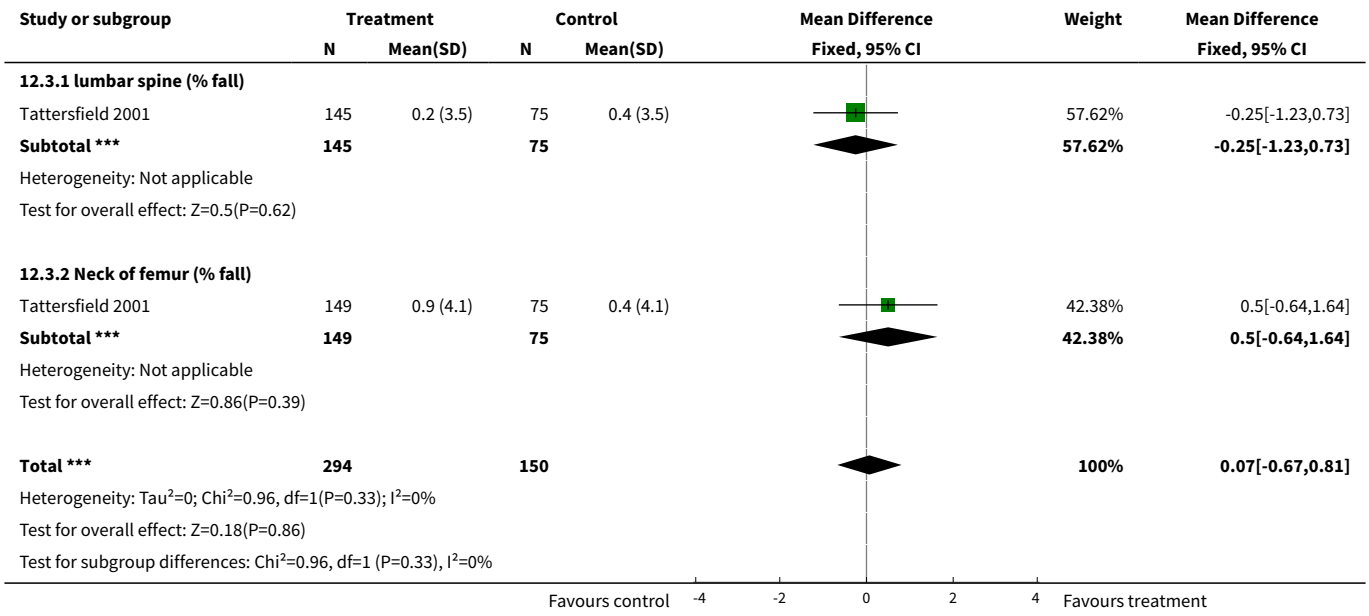
Analysis 12.1. Comparison 12 inhaled steroid vs placebo - Cochrane Concealment C, Outcome 1 Osteocalcin mcg/l, cross-over.



Analysis 12.2. Comparison 12 inhaled steroid vs placebo - Cochrane Concealment C, Outcome 2 Vertebral fracture.



Analysis 12.3. Comparison 12 inhaled steroid vs placebo - Cochrane Concealment C, Outcome 3 Bone mineral density.



WHAT'S NEW

Date	Event	Description
30 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 2, 2002

Date	Event	Description
11 October 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AJ and MB developed the original idea and protocol. All reviewers were involved in selecting abstracts and final papers for inclusion. GR searched alternative databases and JF contacted authors and pharmaceutical companies. MS advised on relevance of outcome measures. KH gave statistical advice and data extraction. JF did data extraction, all entry into Review Manager and analysis. All members contributed to the final document.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of General Practice, University of Wales College of Medicine, UK.

External sources

- Wales Office of Research & Development for Health and Social Care, The National Assembly for Wales, UK.
- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Asthma [*drug therapy] [metabolism]; Bone Density [drug effects]; Bone and Bones [*drug effects] [metabolism]; Glucocorticoids [administration & dosage] [*pharmacology]; Pulmonary Disease, Chronic Obstructive [*drug therapy] [metabolism]

MeSH check words

Female; Humans; Male; Middle Aged