

Cochrane Database of Systematic Reviews

Fluoride for treating postmenopausal osteoporosis (Review)

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[Intervention Review]

Fluoride for treating postmenopausal osteoporosis

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ABSTRACT

Background

Osteoporosis is a condition that results in an increased risk of fractures due to the reduction of bone volume, which is caused by an imbalance between bone formation and bone resorption. Because of this property, fluoride has been used for over 30 years as a treatment for osteoporosis.

Objectives

To assess the efficacy of fluoride therapy on bone loss, vertebral and non-vertebral fractures and side effects in postmenopausal women.

Search methods

We searched MEDLINE, Current Contents and the Cochrane Controlled Trial Registry up to December 1998.

Selection criteria

Two independent reviewers selected RCTs which met predetermined inclusion criteria.

Data collection and analysis

Two reviewers independently extracted data using predetermined forms and assessed the methodological quality of the trials using a validated scale. For dichotomous outcomes, relative risks (RR) were calculated and for continuous outcomes, weighted mean differences (WMD) of percentage change from baseline were calculated. Where heterogeneity existed (determined by a chi-square test) a random effects model was used.

Main results

Eleven studies (1429 subjects) met the inclusion criteria. The increase in lumbar spine bone mineral density (BMD) was found to be higher in the treatment group than in the control group with a WMD 8.1% (95%CI: 7.15,9.09) after two years of treatment and 16.1%(95%CI: 14.65,17.5) after four years. The RR for new vertebral fractures was not significant at two years [0.87 (95%CI: 0.51,1.46)] or at four years [0.9(95%CI: 0.71,1.14)]. The RR for new non-vertebral fractures was not significant at two years 1.2(95%CI: 0.68,2.1) but was increased at four years in the treated group 1.85(95%CI: 1.36,2.5), especially if used at high doses and in a non slow release form. The RR for gastrointestinal side effects was not significant at two years 2.18(95%CI: 0.86,1.21) but was increased at four years in the treated group 2.18(95%CI: 1.69,4.57) especially if fluoride was used at high doses and in a non slow release form. There is no evidence of an important difference in the number of withdrawals and dropouts between treated and control groups at two and four years.



Authors' conclusions

Although fluoride has an ability to increase BMD at lumbar spine, it does not result in a reduction of vertebral fractures. In increasing the dose of fluoride, one increases the risk of non-vertebral fracture and gastrointestinal side effects without any effect on the vertebral fracture rate.

PLAIN LANGUAGE SUMMARY

Fluoride can increase bone mineral density at the lumbar spine, it does not reduce vertebral fractures.

When considering that other therapies have been shown to reduce vertebral fracture rates, fluoride may not be the first choice of therapy for the treatment and prevention of osteoporotic fractures. The evidence showed an increase risk of gastrointestinal side effects and non vertebral fractures with fluoride.



BACKGROUND

Osteoporosis is a condition that results in an increased risk of fractures due to the reduction of bone volume, which is caused by an imbalance between bone formation and bone resorption. It is defined as a disease characterized by low bone mass with microarchitectural deterioration of bone tissue leading to increased bone fragility and consequent increase in fracture risk (CDC 1994). Because of the aging of the general population, osteoporosis is a significant public health problem (Papadimitroupoulos). Furthermore the burden of osteoporotic fractures, in terms of pain, disability and mortality represents a large cost to society (Goeree 1996).

Fluoride is known to stimulate osteoblast activity in humans in contrast to most other drugs used for the prevention and treatment of osteoporosis which inhibit bone resorption (Merz 1981). Because of this property, fluoride has been used for over 30 years as a treatment for osteoporosis (Rich 1961). Histomorphometric studies suggest that although fluoride increases bone mineral density (BMD), there is a corresponding decrease in elasticity and strength of the bone tissue (Aaron 1991), and fluoride is thought to alter the crystalline structure of the bone tissue (Eriksen 1985).

The ability of fluoride to increase BMD has been shown in several randomized controlled trials, as well as a recent systematic review by the National Osteoporosis Foundation (NOF 1998). However, other studies have demonstrated an increase in periarticular pain due to stress fractures (Orcel 1990, Schnitzler 1985) and an increase in the non-vertebral fracture rate with fluoride therapy (Riggs 1994). These side-effects are thought to be related to the type and dosage of fluoride (van Kesteren 1982).

OBJECTIVES

The purpose was to examine the effects of fluoride for the treatment and prevention of postmenopausal osteoporosis in women, with emphasis on the effects of different dosages and types of fluoride.

METHODS

Criteria for considering studies for this review

Types of studies

According to an a priori protocol, we included studies which fulfilled the following eligibility criteria: randomized clinical trials involving women with primary osteoporosis in which the intervention was fluoride in any form or dosage.

For practical reasons, studies published in languages other than English, French or German were not included in the analysis but they were retrieved for further translation. For duplicate or complementary reports of the same trial, the most complete results were used.

Types of participants

We included trials of women with primary osteoporosis.

Types of interventions

We accepted trials of fluoride in any form or dosage, compared to a control group. Acceptable control groups included calcium and vitamin D combinations, if they were given in equal doses to both the control and treatment groups.

Types of outcome measures

Outcome measures included vertebral or non-vertebral fractures, BMD (at any site), pain or height. The selection of outcome measures was based on the consensus report of OMERACT 3 which defined a potential core set of outcomes for osteoporosis (Wells 1997). Biochemical markers were not considered as outcomes for this meta-analysis (Delmas 1993). Where possible, toxicity was analyzed by considering total withdrawals due to adverse reactions and withdrawals for system specific side effects. Individual patient and overall measures of side effects were tabulated, including gastrointestinal side effects (nausea, vomiting, gastritis, diarrhea, gastrointestinal irritation or bleeding) and musculoskeletal side effects (pain and stress fractures). Withdrawals and dropouts were analyzed both overall and for those due to side effects.

Search methods for identification of studies

We searched MEDLINE from January 1966 up to January 1998, the Cochrane Controlled Trials Register (CCTR), Issue 1, 1998 and Current Contents back for six months prior to Jan 1998, using the sensitive search strategy for randomized controlled trials (RCT) recommended by the Cochrane Collaboration Musculoskeletal Group (Haynes 1994). The key words used for this search are described in the appendix and included fluoride, monofluorophosphate, fluoridation, osteoporosis, fractures, bone density and bone loss. Since not all trials are indexed on these electronic data bases, we conducted a hand search of the reference sections of each of the articles retrieved by these searches. We also contacted experts in the field of osteoporosis for help in identifying additional missed studies, unpublished studies, conference proceedings and abstracts.

Data collection and analysis

Two independent reviewers extracted the data, from the original articles (DH, SM). In case of disagreement, a third reviewer (VW) helped reach consensus after consulting the original article. Data extraction was performed using a pre-established form which included aspects of the study design and methodology, intervention characteristics, participant characteristics, adverse events, outcome measures and quality assessment.

Where possible, the mean percent of baseline and the corresponding standard deviation were extracted. In several studies these values were not directly available. Letters were sent to three authors for additional data, and one author of two trials replied (Riggs 1982, Riggs 1990). If only the initial and final bone density was presented, a Taylor's series expansion was used to approximate the standard deviation of the percent change, based on the mean and standard deviation of the initial and final bone density.

Studies with the same comparator were considered together in the meta-analysis. Relative risks (RR) were calculated for dichotomous outcomes such as fractures. For continuous outcomes such as BMD, weighted mean differences (WMD) were calculated. Fixed effects models were used throughout, but random effect models were used for outcomes with significant heterogeneity. Side effects were tabulated and assessed using relative risks. All results using chi square test for heterogeneity were significant if p<0.05.

We investigated whether the differences between individual trials were greater than expected by chance using the Cochran's Q test for

Fluoride for treating postmenopausal osteoporosis (Review)

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heterogeneity (Fleiss 1993). We explored significant heterogeneity using two approaches. First, we conducted an influence analysis in which we assessed whether only one study was responsible for the heterogeneity, by removing each study from the analysis. If only one study led to heterogeneity, we separated the results from the pooled analysis and considered them separately. If more than one study led to heterogeneity, we used a random effects model to present the overall results.

We then explored whether the following factors explained heterogeneity by comparing subgroups: 1) fluoride dosage (low or high dose of fluoride); 2) type of fluoride (monofluorophosphate or sodium fluoride); 3) type and dose of comparator (low dose calcium < 500 mg/day), high dose calcium (>500 mg/day), vitamin D or hormone replacement therapy); 4) inclusion of males; 5) methodological quality (<3 versus > 3); and 6) slow-release and enteric coated formulations. Low dose fluoride was defined as less than 30 mg of elemental fluoride, based on clinical experience (Bardin 1995). The elemental fluoride of sodium fluoride preparations was calculated by the rule: 2.2 mg sodium fluoride are equivalent to 1 mg elemental fluoride. Elemental fluoride composition of MFP was generally given in the corresponding articles.

RESULTS

Description of studies

A total of 752 references were identified using the search strategy in MEDLINE. A further 39 were identified in the CCTR search list. Three additional references were found by searching the reference sections and updating the search strategy. Of these, we retrieved the full articles of 44 studies which appeared to meet the inclusion criteria (Figure 1).

Eleven RCTs met the eligibility criteria for this review (Christiansen 1980, Gambacciani 1995, Grove 1981, Hansson 1987, Kleerekoper 1991, Meunier 1998, Pak 1995, Pak 1995, Reginster 1998, Riggs 1982, Riggs 1990, Sebert 1995). One of these studies (Sebert 1995) included males in its study population, but the men accounted for less than 10% of the population. Therefore this study was included in the analysis and a subgroup analysis was conducted on inclusion of males.

A total of 32 trials were not randomized or did not meet the criteria regarding the intervention group, the control group, the population or the outcomes. Of the excluded trials, 11 were not randomized controlled clinical trials (Dambacher 1976, Dambacher 1986, Harrison 1981, Inkovaara 1973, Inkovaara 1975, Jowsey 1971, Kuntz 1984, Lundy 1995, Pouilles 1991, Power 1986, Resch 1994), nine were retrospective cohort or cross-sectional studies (Affinito 1993, Antich 1993, Dure-Smith 1996, Franke 1974, Jowsey 1972, Jowsey 1975, Resch 1993, Riggs 1973, Zerwekh 1994), six had only histological or biochemical outcomes (Battmann 1997, Eriksen 1985, Erlacher 1994, Gron 1966, Stamp 1990, Zerwekh 1997), two trials compared two active interventions with no placebo group (Hedlund 1989, Mamelle 1988), three trials used only men (Ringe 1987, Ringe 1998, Vose 1978) and one was a non-randomized follow-up of an earlier RCT (Riggs 1994). The other trial was written in Japanese and has not been translated (Takizawa 1980). This trial randomized 87 patients to eight groups with various combinations of sodium fluoride (50 mg), estriol, calcium, vitamin D and one untreated group. After 12 months, significant increases in forearm bone density were found for NaF in combination with calcium and vitamin D as well as for estriol and calcium alone.

The included trials are described in Table 1. The studies included 702 and 727 patients in the intervention and placebo groups, respectively. The women in these trials were all defined as osteoporotic, according to the definition of osteoporosis at the time of the trials (presence of vertebral fractures in earlier trials and low BMD in more recent trials).

Seven trials used sodium fluoride (Na F), three used monofluorophosphate (MFP) and one used both types of fluoride. Two used high dosages of fluoride. All trials used doses of calcium ranging from 400 to 2000 mg per day as an associated treatment. Of these, five used low dose calcium (< 500 mg) and three used high doses (>1000 mg/day). In general, the trials with low dose fluoride also used low dose calcium, with the exception of one study (Hansson). One used enteric-coated fluoride and another used slow release fluoride . Only three used vitamin D. One study included a small proportion of men. Three trials included some women taking hormone replacement therapy . Of these, one study was stratified on HRT, one was not and the Riggs 1982 study, HRT was one of the randomized groups. Christiansen 1980 used three placebo groups to maintain the blinding for ten treatment arms. We considered this trial as two separate trials (one used calcium alone and the other calcium plus vitamin D).

Because the most common study duration was 24 and 48 months, all outcomes were analyzed at these two time points, and when possible, two year data were extracted from the four year studies. Since the differential effect of osteoporosis treatment over time has been shown in a previous meta-analysis (Mackerras 1997), we decided not to combine outcomes for different treatment durations. The fracture and withdrawal data of one three-year trial were pooled with four year data. Only one trial was shorter than 24 months (12 weeks) (Grove 1981), and it was analyzed separately.

One trial achieved the lowest quality score (1), seven trials scored two points, and two trials scored four points. One of the included trials achieved the highest score of five. The median quality score of the included trials was two.

Risk of bias in included studies

Two independent reviewers (DH, SM), using a validated quality assessment instrument (Jadad 1996), assessed the methodological quality of each trial including the quality of randomization, blinding and reporting of withdrawals. The score was given as follows: if the study was described as randomized, one point; if the study was described as double blinded, one point; if there was a description of withdrawals and dropouts, one point; if the method of randomization was described and appropriate, one point ; if the method of double blinding was described and appropriate, one point ; if the method of randomization was not appropriate or if the method of blinding was not appropriate, deduct one point. Differences were resolved by consensus. If needed, a third reviewer was consulted (BS). Quality assessment was not used as a criterion for including studies.

Effects of interventions

BONE MINERAL DENSITY PERCENT OF BASELINE Bone density was increased in the fluoride group at the lumbar spine. The weighted mean difference at this site at two years was

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WMD 8.1 % (95% CI: 7.15, 9.09) and at four years, WMD 16.1% (95% CI: 14.65, 17.5) (random effects model). At the hip at two years the WMD was 3.4% (95% CI: -0.17, 6.91) (random effects model) and at four years it was 5.4% (95% CI: -3.01, 13.93) (random effect model). At the forearm, the fluoride treated group had lower bone density at both two and four years, with WMD of -1.7% (95% CI: -3.09, -3.33) and -3.3%(95% CI: -6.19, -0.46) (random effect model), respectively. The data for total body and trochanter BMD were available in single studies. The WMD difference was in favour of fluoride at both sites: 7.1% (95% CI: 1.06, 13.14) for total body and 15.6% (95% CI: 13.03, 18.18) for femoral trochanter.

Heterogeneity was significant for the lumbar spine at both two and four years. For the analysis at two years, the Riggs 1990 trial (Riggs 1990) led to the heterogeneity. This trial used high doses of both fluoride and calcium. The sensitivity analysis for fluoride dosage indicated that dosage could be an explanation for this heterogeneity with a WMD 8.1% (95% CI: 7.1, 9.1) for low doses of fluoride and WMD 20.5% (95% CI: 18.5, 22.6) for high doses. The sensitivity analysis on calcium dosage led to a similar result, mostly due to the fact that trials which used low dose calcium also used low dose fluoride. In the low calcium dose subgroup analysis the WMD was 8.1% (95% CI: 7.0, 9.1). It was 20.1% (95% CI: 18.1, 22.1) in the high calcium dose subgroup analysis. For the four year analysis none of the three trials (Pak 1995, Reginster 1998, Riggs 1990, Sebert 1995), alone, could explain the heterogeneity. The included trials and their distribution between high or low dose fluoride and presence or absence of concurrent HRT (as well as the statistical results) were identical. High dose fluoride, as well as absence of HRT, showed a difference in spine BMD of 36.9% (95% CI: 33.7, 40.01) compared to a WMD of 13.8% (95% CI: 5.8, 21.8) for the two studies with low dose fluoride and presence of HRT. The study with a calcium dose of 1500 mg found a larger increase in spine BMD of 36.9% (95% CI: 33.7, 40.01) compared to a WMD of 10.8% (95% CI: 9.2, 12.4) for calcium 500-1000 mg per day. Here again, the included studies and their distribution between NaF or MFP and low or high quality score as well as the statistical results were identical. The WMD was higher in the NaF low quality subgroup 28.15% (95%CI: 10.2, 45.9) than in the MFP/high quality subgroup 10.4% (95% CI: 8.8, 12.0).

FRACTURES

The overall analysis did not demonstrate a significant difference in the pooled relative risk for vertebral fractures: RR 0.87 (95% CI: 0.51, 1.46) at two years (4 RCTs, N=742) and 0.90 (95% CI: 0.71, 1.14) at four years with 5 RCTs and a total of 646 patients randomized. Significant heterogeneity could not be explained by any subgroup analyses at two years. However, the subgroup analysis at four years showed that the dose of calcium, dose of fluoride, and concurrent HRT treatment were significant. The trials which used low dose fluoride also used low-dose calcium (Pak 1995, Pak 1995, Reginster 1998), with the exception of (Hansson 1987) where 1000 mg/day of calcium was classified as high dose for this comparison. Low dose calcium and low dose fluoride were associated with a reduced risk of fracture (RR 0.29 (95%CI: 0.14, 0.58), and there was no evidence of an important effect of higher dose of fluoride and calcium, compared to placebo (RR 1.0 (95%CI: 0.8, 1.3). For the three trials where HRT was allowed in some women (i.e. not an exclusion criteria) (Pak 1995, Pak 1995, Reginster 1998, Riggs 1982), the pooled fluoride arm demonstrated a reduction in vertebral fractures with a RR 0.30 (95%CI: 0.15, 0.71). There was no statistical difference

between fluoride and the control group for height with a WMD 0.36 (95%CI: -0.10, 0.82).

For non-vertebral fractures, the relative risk was not significantly different from placebo at two years (RR 1.20 (95%CI: 0.68, 2.10). No subgroup analysis led to different results. However, at four years, the relative risk of non vertebral fractures was increased with fluoride with a RR 1.85 (95%CI: 1.36, 2.50). However, the relative risk of non vertebral fracture was not significantly different than placebo for low-dose fluoride, low dose calcium (as for vertebral fractures, the trials with high dose fluoride also used high dose calcium), high quality trials, use of HRT or use of slow released fluoride.

WITHDRAWALS AND SIDE EFFECTS

Overall, 19% of patients in these trials withdrew from the study by the end of two years and 28% by the end of four years. Fluoride withdrawals were not statistically different from control with a RR 1.0 (95%CI: 0.64, 1.56) at two years and 1.0 (95%CI: 0.78, 1.29) at four years.

At two years, there was no significant increase in the risk of gastrointestinal side effects, including dyspepsia, nausea, diarrhea, and vomiting with a RR of 1.02 (95% CI: 0.86, 1.21) and no significant heterogeneity. No subgroup analyses were significant. At four years, the fluoride group was at a higher risk for GI side effects with an RR of 2.18 (95% CI: 1.69, 4.57). The risk for GI side effects was not statistically different when compared to placebo for low dose fluoride as well as low dose calcium (which correspond to the same studies), presence of HRT in the treatment groups, high quality and slow-release fluoride.

Lower limb pain syndrome was significantly increased with fluoride with a RR of 3.5 (95%CI: 1.74, 7.04) without heterogeneity at two years but at 3.11 (95%CI: 0.81, 11.87) at four years with significant heterogeneity (chi-square =21.9, df=3). This heterogeneity is likely due to the wide variety of definitions of lower limb pain. Because of doubt about clinical relevance and similarity of these various definitions, no subgroup analyses were attempted.

DISCUSSION

In this meta-analysis we found that fluoride increased the bone mineral density without any efficacy on the incidental vertebral fractures. Since no trial compared fluoride to placebo without calcium, it is more difficult to assess the true effect of fluoride on BMD or fractures. Furthermore, the subgroup analysis conducted on dosage of calcium provided different results than the overall analysis. This meta-analysis confirmed the well-known increase in lumbar BMD with fluoride (Hansson 1987). The heterogeneity in this outcome is easily explained by the presence of Riggs's trial (Riggs 1990) in which fluoride was used at high dose, as shown in the subgroup analysis on fluoride or calcium dosage. Forearm bone density was actually lower in the fluoride groups at both two and four years. Since the forearm has a different composition of trabecular and cortical tissue, this differential effect might be expected. There was no effect of fluoride on BMD at the femoral neck. Furthermore, the measurement of BMD at forearm is now more precise and changes at this site may be detected. By comparison, the measurement at the hip is less precise. A greater number of patients may be needed to show differences.



Fluoride showed no effect on vertebral fracture rate, neither after two years of treatment nor after four years. At the two years period, the subgroup analysis did not show any different results. But, at four years there was a statistically significant reduction in the risk with 1) low dose fluoride; 2) presence of HRT in the treatment groups; 3) use of a slow-release formulation and 4) low dose calcium. The effects of the dosage of calcium and fluoride cannot be determined independently in this meta-analysis, as low dose fluoride was always administered with low dose calcium with the exception of one small trial (Hansson 1987). As Shea et al have shown, (Shea 1999), calcium has a small but significant effect on bone loss and the magnitude of the reduction in fracture risk due to calcium alone remains uncertain. We would suggest that most of the effect on fracture risk was attributable to fluoride and that both fluoride and calcium were required to reduce the risk of vertebral fracture. Furthermore, the effects of HRT cannot be determined independently, as it is present in the two largest trials with low dose calcium and fluoride (Pak 1995, Pak 1994a, Reginster 1998). The positive effect on vertebral fractures was significant in only one trial (and two publications) by Pak (Pak 1995, Pak 1994a). This trial used a low dose, slow-release, sodium fluoride, with low dose calcium (500 mg/day) and allowed the presence of HRT in the treatment groups. For the women taking HRT, there was no difference between fluoride and control (75% in 16 vs 76.9% in 13). In contrast, in the women not taking HRT, there was a higher vertebral fracture-free rate in the fluoride compared to the control group (85.7% in 35 vs 60% in 35 which is significant).

A possible explanation for the lack of effect of high dose fluoride on non vertebral fracture rates is that fluoride increases the thickness of bone, but decreases bone quality (Aaron 1991). Therefore, fluoride would not be expected to prevent fractures, but would increase bone density. The most plausible explanation of the differential effect of different doses of fluoride is that high dose and non-enteric coated fluoride have twice the under curve surface, which leads to toxic concentrations of fluoride in the bone tissue (Sakhaee 1991). Patients treated for four years with such high doses of fluoride could have a toxic bone concentrations of fluoride which could modify both trabecular and compact bone leading to an increase in both the non vertebral and vertebral fracture rate (Lees 1992). Height is known to be a responsive endpoint for osteoporosis (Cranney 1999) and it is correlated with the number of crushed vertebrae. Therefore, it is not surprising that the results about the effect on height in our analysis went in the same direction as the results on vertebral fracture.

Furthermore, low dose calcium and fluoride (as well as the uncontrolled presence of HRT) were not associated with an increased risk of non vertebral fractures or GI side effects. In contrast, high doses of fluoride and concurrent calcium were associated with an increased risk of non vertebral fractures and GI side effects.

Heterogeneity was significant for bone density and fracture outcomes. The main differences between studies could be explained by the dose of concurrent calcium and the dose of fluoride. Unfortunately, since the same trials with high-dose fluoride also used a high dose of calcium, it is impossible to determine which factors are responsible for the differential effect with lower dosages.

By using percentage change of BMD, we attempted to control for different machines, baseline BMD and assessment methods

(Faulkner 1996). We were able to use figures to extrapolate the mean % change at two and four years. This technique increases the sample size, at the risk of inaccurate results. In one case (Riggs 1990), we received the numerical data in tabular form from the author and found the estimated values from the graph were within 4% of the results provided by the author.

All participants had established osteoporosis defined by either low BMD or prevalent fractures. A subgroup analysis conducted on the definition of osteoporosis (incident fractures versus BMD criteria) demonstrated no significant difference in the effect on vertebral fractures, non vertebral fractures or lumbar BMD at two or four years. In one study (Sebert 1995), the population included 4% men. We found no difference in the results of this trial compared to the pooled analysis for any outcome. Duration of treatment was not explored as an explanation of the differences between the trials since the effect of time on bone mineral density measurement has been demonstrated by Mackerras et al (Mackerras 1997). Therefore, data was analyzed separately at two major endpoints: two and four years. The results of this meta-analysis suggest that the difference in bone density is higher after four years than after two years of treatment, confirming longitudinal follow-up studies which have also demonstrated this (Pak 1995, Riggs 1994).

Some of the between-trial differences for lower limb pain are likely due to different definitions of lower limb pain which included "lower extremity pain", "joint pain", "lower limb pain" and "osteoarticular minor manifestation". Although differences existed between trials, fluoride was associated with significantly more lower limb pain in this meta-analysis, but subgroup analysis were not attempted due to uncertainty about the clinical similarity of the various definitions of this outcome. Some histomorphometric studies (Boivin 1991) have confirmed that the accumulation of fluoride in certain bone sites worsens microfractures due to fluoride-induced hyperosteoidosis, which interferes with the normal bone healing processes. It is now widely recognized that the lower limb pain syndrome (Orcel 1990) is related to the presence of bone fissures. This was confirmed in the study by Meunier et al (Meunier 1998), where lower limb pain syndrome was related to the presence of radiological evidence of microfractures or fractures on bone scintigraphy. Since high dose fluoride was associated with an increased risk of non vertebral and vertebral fractures, it is not surprising that a high rate of fluoride-associated lower limb pain was reported by the Riggs et al 1990 (Riggs 1990) study which used a high fluoride dose. We were unable to validate previous hypotheses that lower limb pain is more frequent with NaF than MFP (Delmas 1990).

Sodium fluoride, especially at high doses and in a non-enteric coated form, is converted to fluoric acid and adheres on the gastric wall (Muller 1992). Therefore, the enteric-coated sodium fluoride should cause less gastrointestinal side effects than plain sodium fluoride. In our analysis we have shown that there was no difference between treated and controlled patients when considering the gastrointestinal minor side effects. At two years, no subgroup analyses were significant, including those examining the type of fluoride and enteric preparation. The slow-release formulation was associated with a lower risk for GI side effects at four years. At four years, the high dose fluoride was associated with a significantly higher risk compared to placebo, in contrast to the low dose trials.

In this meta-analysis of 11 RCTs, including 1429 patients, on the efficacy and side effects of fluoride in the postmenopausal



osteoporosis, we can conclude that fluoride increases significantly the BMD at the lumbar spine after two and four years of treatment. The number of patients with a new vertebral fracture was not different from placebo after two or four years of fluoride treatment, but the concurrent use of HRT and/or of low fluoride doses led to better results for fluoride. Furthermore there was no evidence that the use of MFP versus NaF affected the RR. The RR of nonvertebral fracture was not influenced by fluoride after two years of treatment. After four years of treatment, the risk of non-vertebral fractures was increased, except in the case of the use of HRT, low fluoride doses and/or slow released fluoride. At two years, the frequency of GI side effects was not influenced by fluoride but after four years of treatment the results were different with an increased risk of GI side effect, except when HRT, low fluoride doses and slow released fluoride were used. In conclusion, fluoride increases BMD without any evidence of important impact on vertebral fracture rate. This occurs even if the use of low doses or of slow released fluoride does not increase the risk of non-vertebral fracture (or GI side effects). Considering that other therapies, such as estrogens, raloxifene (Ettinger 1999) and bisphosphonates, have been shown to reduce vertebral fracture rates (NOF 1998), fluoride may not be the first choice of therapy for the treatment or prevention of osteoporotic fractures.

AUTHORS' CONCLUSIONS

Implications for practice

Considering that other therapies, such as estrogens, raloxifene and bisphosphonates, have been shown to reduce vertebral fracture rates (NOF), fluoride may not be the first choice of therapy for the treatment or prevention of osteoporotic fractures.

Implications for research

Although fluoride increases bone mineral density, the evidence from randomized controlled trials shows that fluoride does not reduce the risk of vertebral fractures. This conclusion was consistent for both monofluorophosphate and sodium fluoride. Furthermore, we found evidence of increased risk of gastrointestinal side effects and non vertebral fractures with fluoride.

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REFERENCES

References to studies included in this review

Christiansen 1980 {published data only}

Christiansen C, Christensen MS, McNair P, et al. Prevention of early postmenopausal bone loss: controlled 2-year study in 315 normal females.. *Eur J Clin Invest* 1980;**10**(4):273-279.

Gambacciani 1995 {published data only}

Gambacciani M, Spinetti A, Taponeco F, et al. Treatment of postmenopausal vertebral osteopenia with monofluorophospate: a long-term calcium-controlled study. *Osteoporosis International* 1995;**5**(6):467-471.

Grove 1981 {published data only}

Grove O, Halver B. Relief of osteoporotic backache with fluoride, calcium, and calciferol. *Acta Med Scand* 1981;**209**(6):469-471.

Hansson 1987 {published data only}

Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int* 1987;**40**(6):315-317.

Kleerekoper 1991 {published data only}

Kleerekoper M, Peterson EL, Nelson DA, et al. A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporos Int* 1991;**1**(3):155-161.

Meunier 1998 {published data only}

Meunier PJ, Sebert JL, Reginster JY, et al. Fluoride salts are no better at preventing new vertebral fractures than calciumvitamin D in postmenopausal osteoporosis: the FAVOStudy. *Osteoporos Int* 1998;**8**:4-12.

Pak 1994a {published data only}

Pak CY, Sakhaee K, Piziak V, et al. Slow-release sodium fluoride in the management of postmenopausal osteoporosis. A randomized controlled trial [see comments]. *Ann Intern Med* 1994;**120**(8):625-632.

Pak 1995 {published data only}

Pak CY, Sakhaee K, Adams-Huet B, et al. Treatment of postmenopausal osteoporosis with slow-release sodium fluoride. Final report of a randomized controlled trial [see comments]. *Ann Intern Med* 1995b;**123**(6):401-408.

Reginster 1998 {published data only}

Reginster JY, Meurmans L, Zegels B, et al. The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized, controlled trial. *Ann Intern Med* 1998;**129**(1):1-8.

Riggs 1982 {published data only}

Riggs BL, Seeman E, Hodgson SF, Taves DR, O'Fallon WM. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. Comparison with conventional therapy. *N Engl J Med* 1982;**306**(8):446-450.

Riggs 1990 {published data only}

Riggs BL, Hodgson SF, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;**322**(12):802-809.

Sebert 1995 {published data only}

Sebert JL, Richard P, Mennecier I, Bisset JP, Loeb G. Monofluorophosphate increases lumbar bone density in osteopenic patients: a double-masked randomized study. *Osteoporos Int* 1995;**5**(2):108-114.

References to studies excluded from this review

Affinito 1993 {published data only}

Affinito P, Di CC, Primizia M, et al. A new fluoride preparation for the prevention of postmenopausal osteoporosis: calcium monofluorophosphate. *Gynecological Endocrinology* 1993;**7**(3):201-205.

Antich 1993 {published data only}

Antich PP, Pak CY, Gonzales J, et al. Measurement of intrinsic bone quality in vivo by reflection ultrasound: correction of impaired quality with slow-release sodium fluoride and calcium citrate.. *Journal of Bone & Mineral Research* 1993;**8**(3):301-311.

Battmann 1997 {published data only}

Battmann A, Resch H, Libanati CR, et al. Serum fluoride and serum osteocalcin levels in response to a novel sustainedrelease monofluorophosphate preparation: comparison with plain monofluorophosphate. *Osteoporosis International* 1997;**7**(1):48-51.

Dambacher 1976 {published data only}

Dambacher MA, Haas HG. [Fluoride therapy of osteoporosis]. [German].. *Deutsche Medizinische Wochenschrift* 1976;**101**(13):504-506.

Dambacher 1986 {published data only}

Dambacher MA, Ittner J, Ruegsegger P. Long-term fluoride therapy of postmenopausal osteoporosis. *Bone* 1986;**7**(3):199-205.

Eriksen 1985 {published data only}

Eriksen EF, Mosekilde L, Melsen F. Effect of sodium fluoride, calcium, phosphate, and vitamin D2 on trabecular bone balance and remodeling in osteoporotics. *Bone* 1985;**6**(5):381-389.

Erlacher 1994 {published data only}

Erlacher L, Teufelsbauer H, Bernecker P, Pietschmann P, Weissel M. Comparison of serum fluoride levels after administration of monofluorophosphate-calcium carbonate or sodium fluoride: differences in peak serum concentrations. *Clinical Investigator* 1994;**72**(12):1082-1085.

Hedlund 1989 {published data only}

Hedlund LR, Gallagher JC. Increased incidence of hip fracture in osteoporotic women treated with sodium fluoride. *Journal of Bone & Mineral Research* 1989;**4**(2):223-225.

Fluoride for treating postmenopausal osteoporosis (Review)



Inkovaara 1973 {published data only}

Inkovaara J, Hanhijarvi H, Iisalo E, Jarvinen K. Fluoride and osteoporosis. *British Medical Journal* 1973;**1**(853):613-.

Inkovaara 1975 {published data only}

Inkovaara J, Heikinheimo R, Jarvinen K, et al. Prophylactic fluoride treatment and aged bones. *British Medical Journal* 1975;**3**(5975):73-74.

Jowsey 1971 {published data only}

Jowsey J, Riggs BL, Kelly PJ, Hoffman DL. Effect of combined therapy with sodium fluoride, vitamin D, and calcium in osteoporosis. *Journal of Laboratory & Clinical Medicine* 1971;**78**(6):994-995.

Jowsey 1972 {published data only}

Jowsey J, Riggs BL, Kelly PJ, Hoffmann DL. Effect of combined therapy with sodium fluoride, vitamin D and calcium in osteoporosis. *American Journal of Medicine* 1972;**53**(1):43-49.

Jowsey 1975 {published data only}

Jowsey J, Riggs BL. Letter: Prophylactic fluoride treatment and aged bones. *British Medical Journal* 1975;**3**(5986):766-.

Riggs 1973 {published data only}

Riggs BL, Jowsey J, Kelly PJ, Hoffman DL, Arnaud CD. Studies on pathogenesis and treatment in postmenopausal and senile osteoporosis. *Clinics in Endocrinology & Metabolism* 1973;**2**(2):317-332.

Riggs 1994 {published data only}

Riggs BL, O'Fallon WM, Lane A, et al. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. *J Bone Miner Res* 1994;**9**(2):265-275.

Ringe 1987 {published data only}

Ringe JD. [Combined fluoride therapy for primary osteoporosis. Results of two-years' treatment with sodium monofluorophosphate and calcium]. [German]. *Fortschritte der Medizin* 1987;**105**(19):379-382.

Ringe 1998 {published data only}

Ringe JD, Drost DJ, Kipshoven C, Rovati LC, Setnikar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and lowdose intermittent monofluorophosphate. *Osteoporos Int* 1998;**8**:47-52.

Takizawa 1980 {published data only}

Takizawa H, Igarashi M, Hayashi Y, Karube S, Kimura H. [Comparison of treatments in senile osteoporosis: follow up for 12 months (author's transl)]. [Japanese]. Journal of the Japanese Orthopaedic Association - Nippon Seikeigeka Gakkai Zasshi 1980;**54**(4):345-355.

Vose 1978 {published data only}

Vose GP, Keele DK, Milner AM, et al. Effect of sodium fluoride, inorganic phosphate, and oxymetholone therapies in osteoporosis: a six year progress report. *J Gerontol* 1978;**33**:204-212.

Additional references

Aaron 1991

Aaron JE, de VC, Kanis JA. The effect of sodium fluoride on trabecular architecture. *Bone* 1991;**12**(5):307-310.

Bardin 1995

Bardin T, Kuntz D. [Medicaments stimulant la formation osseuse]. In: Medicine-Sciences Flammarion, editor(s). Therapeutique Rhumatologique. Paris, 1995:105-111.

Boivin 1991

Boivin G, Grousson B, Meunier PJ. X-rays microanalysis of fluoride distribution in microfracture calluses in cancellous iliac bone from osteoporotic patients treated with fluoride and untreated. *J Bone Miner Res* 1991;**6**:1183-1190.

CDC 1994

Anonymous. Consensus Development Conference: Diagnosis, prophylaxis and treatment of osteroporosis. *Am J Med* 1994:646-650.

Cranney 1999

Cranney A, Welch V, Tugwell P, et al. Responsiveness of endpoints in osteoporosis clinical trials-an update. *J Rheumatol* 1999;**26**:222-228.

Delmas 1990

Delmas PD, Dupuis J, Duboeuf F, Chapuy MC, Meunier PJ. Treatment of vertebral osteoporosis with disodium monofluorophosphate: comparison with sodium fluoride. *J Bone Miner Res* 1990;**5**(Suppl 1):S143-S147.

Delmas 1993

Delmas PD. Biochemical markers of bone turnover: theoretical considerations and clinical use in osteoporosis. *Am J Med* 1993;**8**:348-354.

Dure-Smith 1996

Dure-Smith BA, Farley SM, Linkhart SG, Farley JR, Baylink DJ. Calcium deficiency in fluoride-treated osteoporotic patients despite calcium supplementation. *Journal of Clinical Endocrinology & Metabolism* 1996;**81**(1):269-275.

Ettinger 1999

Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;**282**(7):637-645.

Faulkner 1996

Faulkner KG, Roberts LA, McCung MR. Discrepancies in normative data between Lunar and Hologic DXA sustems. *Osteoporos Int* 1996;**6**:432-436.

Fleiss 1993

Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;**2**(2):121-145.

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Franke 1974

Franke J, Rempel H, Franke M. Three years' experience with sodium-fluoride therapy of osteoporosis. *Acta Orthopaedica Scandinavica* 1974;**45**(1):1-20.

Goeree 1996

Goeree R, O'Brien B, Pettit D, et al. An assessment of the burden of illness due to osteoporosis in Canada. *Journal SOGC* 1996, (Suppl):15-24.

Gron 1966

Gron P, McCann HG, Bernstein D. Effect of fluoride on human osteoporotic bone mineral. A chemical and crystallographic study. *Journal of Bone & Joint Surgery - American Volume* 1966;**48**(5):892-898.

Harrison 1981

Harrison JE, McNeill KG, Sturtridge WC, et al. Three-year changes in bone mineral mass of postmenopausal osteoporotic patients based on neutron activation analysis of the central third of the skeleton. *Journal of Clinical Endocrinology & Metabolism* 1981;**52**(4):751-758.

Haynes 1994

Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Info Assoc* 1994;**1**(6):447-458.

Jadad 1996

Jadad AR, Moore RA, Carrol D. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials* 1996;**17**:1-12.

Kuntz 1984

Kuntz D, Marie P, Naveau B, et al. Extended treatment of primary osteoporosis by sodium fluoride combined with 25 hydroxycholecalciferol. *Clinical Rheumatology* 1984;**3**(2):145-153.

Lees 1992

Lees S, Hansson T. Effect of fluoride dosage on bone density, sonic velocity and longitudinal modules of rabbits femur. *Calcif Tissue Int* 1992;**50**:88-92.

Lundy 1995

Lundy MW, Stauffer M, Wergedal JE, et al. Histomorphometric analysis of iliac crest bone biopsies in placebo-treated versus fluoride-treated subjects [see comments]. *Osteoporosis International* 1995;**5**(2):115-129.

Mackerras 1997

Mackerras D, Lumley T. First- and second-year effects in trials of calcium supplementation on the loss of bone density in postmenopausal women. *Bone* 1997;**21**(6):527-533.

Mamelle 1988

Mamelle N, Meunier PJ, Dusan R, et al. Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988;**2**(8607):361-365.

Merz 1981

Merz W. The essential trace elements. *Science* 1981;**213**(1332-1338).

Muller 1992

Muller P, Schmid K, Warnecke G, Stnikar I, Simon B. Sodium fluoride induced gastric mucosal lesions: comparison with sodium monofluorophosphate. *Zeitung Gastroenterology* 1992;**30**(252-254).

Mulrow 1997

Mulrow CD, Oxman ADe. Oxford: Update Software; 1997. Cochrane Collaboration Handbook [updated September 1997]. 1997;**September 1997 update**.

NOF 1998

National Osteoporosis Foundation. Osteoporosis: Review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis, status report. *Osteoporos Int* 1998, (Suppl 4):S1-S88.

Orcel 1990

Orcel P, de VC, Prier A, et al. Stress fractures of the lower limbs in osteoporotic patients treated with fluoride. *J Bone Miner Res* 1990;**5**(Suppl 1):S191-S194.

Papadimitroupoulos

Papadimitroupoulos EA, Coyte PC, Josse RG, Greenwood CE. Current and projected rates of hip fractures in Canada. *CMAJ* 1997;**157**(10):1537-1566.

Pouilles 1991

Pouilles JM, Tremollieres F, Causse E, Louvet JP, Ribot C. Fluoride therapy in postmenopausal osteopenic women: effect on vertebral and femoral bone density and prediction of bone response. *Osteoporos Int* 1991;**1**(2):103-109.

Power 1986

Power GR, Gay JD. Sodium fluoride in the treatment of osteoporosis. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 1986;**9**(1):41-43.

Resch 1993

Resch H, Libanati C, Farley S, et al. Evidence that fluoride therapy increases trabecular bone density in a peripheral skeletal site. *Journal of Clinical Endocrinology & Metabolism* 1993;**76**(6):1622-1624.

Resch 1994

Resch A, Pietschmann F, Bernecker P, et al. [Evidence of fluoride-induced effects on the calcaneus by measurements of broadband ultrasound attenuation (BUA)]. [German]. *Rofo.Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgebenden Verfahren* 1994;**161**(6):547-550.

Rich 1961

Rich C, Ensinck J. Effect of sodium fluoride on calcium metabolism in human beings. *Nature* 1961;**194**:184-185.



Sakhaee 1991

Sakhaee K, Pak CY. Fluoride bioavailability from immediatereleased fluoride with calcium carbonate compared with slow release sodium fluoride with calcium citrate. *J Bone Miner Res* 1991;**14**:131-136.

Schnitzler 1985

Schnitzler CM, Solomon L. Trabecular stress fractures during fluoride therapy for osteoporosis. *Skeletal Radiology* 1985;**14**(4):276-279.

Shea 1999

Shea B, Guyatt G, Cranney A, et al. Meta-Analysis of Calcium Supplementation for the Prevention of Postmenopausal Osteoporosis. *Arch Intern Med* 1999;**Submitted**.

Stamp 1990

Stamp TC, Saphier PW, Loveridge N, et al. Fluoride therapy and parathyroid hormone activity in osteoporosis. *Clinical Science* 1990;**79**(3):233-238.

van Kesteren 1982

Christiansen 1980

van Kesteren RG, Duursma SA, Visser WJ, et al. Fluoride in bone and serum during treatment of osteoporosis with sodium fluoride, calcium and vitamin D. *Metab Bone Dis* 1982;**4**:31-37.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Wells 1997

Wells G, Cranney A, Shea B, Tugwell P. Responsiveness of Endpoints in Osteoporosis Clinical Trials. *J Rheumatol* 1997;**24**(6):1230-1233.

Zerwekh 1994

Zerwekh JE, Hagler HK, Sakhaee K, et al. Effect of slow-release sodium fluoride on cancellous bone histology and connectivity in osteoporosis. *Bone* 1994;**15**(6):691-699.

Zerwekh 1997

Zerwekh JE, Padalino P, Pak CY. The effect of intermittent slow-release sodium fluoride and continuous calcium citrate therapy on calcitropic hormones, biochemical markers of bone metabolism, and blood chemistry in postmenopausal osteoporosis. *Calcif Tissue Int* 1997;**61**:272-278.

References to other published versions of this review

Haguenauer 2000

Haguenauer D, Welch V, Shea B, Tugwell P, Adachi JD, Wells G. Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. *Osteoporosis International* 2000;**11**(9):727-38.

Methods	RCT duration 24 months10 groups for randomisation. 56 patients in 2 fluoride groups and 259 in 8 con- trol groups	
Participants	315 post menopausal v	vomen Denmark
	age 50.1 time since me race NA	nopause 19.1 months
Interventions	Na F 9 mg element (lov sus HRT Thiazides, vit I	v dose), non enteric coated, non slow-releaseassociated treatment calciumver- D or 1 alpha vit D
Outcomes	%change in BMC forea	rm
Notes	quality score 4 randomization 2 blinding 1 withdrawals and dropouts 1	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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Gambacciani 1995

Methods	RCT duration 24 months30 patients in the fluoride group, 30 in the control group	
Participants	60 postmenopausal osteopenic women in Italy age 51.6 52.3 in each group race NA years since menopause [2-5] natural menopause 100%	
Interventions	MFP 20 mg element flu associated treatment c	oride (low dose), non enteric-coated, non slow-release calciumversus placebo
Outcomes	BMD lumbar, total bod GI side effects	y, legs, arms
Notes	quality score 2 randomization 1 blinding 0 withdrawals and dropouts 1	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Grove 1981

Methods	RCT duration 3 months14 patients in each group	
Participants	28 postmenopausal wo	omen with backpain and vertebral fracture
	age 73.9 menopause di race NA	uration NA
Interventions	NaF 9 mg fluoride elem associated treatment c	nent (low dose), non enteric-coated, non slow-release calcium plus vitamine Dversus placebo
Outcomes	forearm cnange in BMC	C, pain sore, strenght score, metacarpal index
Notes	quality score 2 randomization 1 blinding 0 withdrawals and dropo	outs 1
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hansson 1987

Methods	RCT duration 36 months25 patients in each treated and placebo group
Participants	100 osteoporotic postmenopausal women in Sweden

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H	an	sson	1987	(Continued)
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	age 66 duration of mer race NA	nopause NA
Interventions	Na F 4.5 or 13.6 fluoride element (low dose), non enteric-coated, non slow-release associated treatment calcium versus placebo or calcium	
Outcomes	Lumbar BMC	
Notes	quality score 2 randomization 1 blinding 0 withdrawals and drope	outs 1
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kleerekoper 1991

Methods	RCT duration 48 months46 patients in fluoride group, 38 in control group
Participants	84 post menopausal osteoporotic women, in USA age 66.2 duration of menopause 21.4 race 100% caucasian
Interventions	Na F 34 mg fluoride element (high dose), non enteric-coated, non slow release associated treatment calciumversus placebo
Outcomes	vertebral fractures, non vertebral fractures, height, forearm BMD, GI side effects
Notes	quality score 4 randomization 1 blinding 2 withdrawals and dropouts 1
Risk of bias	

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

Meunier 1998

Methods	RCT duration 24 months208 patients in fluoride group and146 in control group
Participants	354 postmenopausal osteoporotic women in France age 65.7 durtation of menopause NA race 100% caucasian

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Meunier 1998 (Continued)				
Interventions	Na F 22.6 mg fluoride element (low dose) enteric coated, non slow release,versus MFP 19.8 mg or 26.4 mg element fluoride (low doses), non enteric coated, non slow-releaseassociated treatment calcium plus vitamine Dversus placebo			
Outcomes	vertebral and non verte side effects	ebral fractures, lumbar and femoral neck BMD, lower limb pain syndrome and GI		
Notes	quality score 2 randomization 1 blinding 0 withdrawals and drope	puts 1		
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Allocation concealment?	Unclear risk	B - Unclear		

Pak 1994a

Methods		
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Pak 1995

Methods	RCT duration 48 months54 patients in fluoride group and 56 in control group
Participants	110 postmenopausal osteoporotic women in USA age 67.6 duration of menopause 19.2 race NA
Interventions	Na F 27.5 mg element (low dose), non enteric-coated, slow -releaseassociated treatment calcium with or without HRTversus placebo
Outcomes	vertebral and non vertebral fractures , BMD femoral neck and forearm, BMC lumbar, GI side effects
Notes	quality score 2 randomization 1 blinding 0

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Pak 1995 (Continued)

withdrawals and dropouts 1

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

Reginster 1998

Methods	RCT duration 4 years ir	n Belgium ; outpatients100 patients in each treated and control groups	
Participants	200 White postmenopausal women : ; with BMD <= 2.5 T-Score regardless to any previous fractures ex- cept hip ; mean age 63.5 ; mean age at menopause 48.5		
Interventions	MPF 20 mg Fluoride el calcium 1000mgversus	ement (low dose), non enteric-coated, non slow-release associated treatment s placebo	
Outcomes	Fractures : - vertebral a BMD : - lumbar and tot	and non vertebral al hip	
Notes	Quality score 5 randomization 2 blinding 2 withdrawals and drope	outs 1	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Allocation concealment?	Low risk	A - Adequate	

Riggs 1982

Methods	RCT duration 4 years approximatively61 patient in 2 fluoride groups and 104 in 3 control groups			
Participants	165 postmenopausal osteoporotic women in USA 5 groups of randomization			
Interventions	Na F 27.5 mg element (low dose), non enteric-coated, non slow-releasewith or without calciumversus placebo, calcium, or ostrogen			
Outcomes	vertebral fractures, GI side effects			
Notes	quality score 1 randomization 0 blinding 0 withdrawals and dropouts 1			
Risk of bias				
Bias	Authors' judgement Support for judgement			

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Riggs 1982 (Continued)

Allocation concealment?

Unclear risk

B - Unclear

Riggs 1990

Methods	RCT duration 48 months101 patients in each fluoride and control group		
Participants	202 postmenopausal osteoporotic women in USA age 68 duration of menopause 21.25 race 100% caucasian		
Interventions	Na F, 41.25 mg fluoride associated treatment o	e element (high dose), non enteric-coated, non slow-releaseversus placebo calcium	
Outcomes	lumbar BMD, vertebral effects	l and non vertebral fractures, BMD femoral neck and femoral trochanter , GI side	
Notes	quality score 2 randomization 1 blinding 0 withdrawals and drope	outs 1	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Allocation concealment?	Unclear risk	B - Unclear	

Sebert 1995

Methods	RCT duration 24 months35 patients in fluoride group and 41 in control group
Participants	94 osteoporotic men and women (% of men 4) in France age 60.35 duration of menopause NA race NA
Interventions	MFP 26.4 mg fluoride element (low dose), non-enteric-coated, non slow-releaseversus placebo associated treatment calcium
Outcomes	lumbar BMD, vertebral and non vertebral fractures, lwr limb pain syndrome, GI side effects
Notes	quality score 2 randomization 1 blinding 1 withdrawals and dropouts 0
Risk of bias	

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

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Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion		
Affinito 1993	Opened trial		
Antich 1993	Cohort study		
Battmann 1997	Biochemical outcomes only		
Dambacher 1976	Opened trial		
Dambacher 1986	Not an RCT		
Eriksen 1985	Not an RCT		
Erlacher 1994	Biochemical outcomes only		
Hedlund 1989	Fluoride therapy present in both groups of randomization.		
Inkovaara 1973	Not an RCT		
Inkovaara 1975	Not an RCT		
Jowsey 1971	Duplicate publication		
Jowsey 1972	Duplicate publication		
Jowsey 1975	Not an RCT		
Riggs 1973	Not an RCT		
Riggs 1994	Non randomized end of a RCT		
Ringe 1987	Combination therapy		
Ringe 1998	Population : only men		
Takizawa 1980	Written in Japanese		
Vose 1978	Population : men only		

DATA AND ANALYSES

Comparison 1. Fluoride vs Placebo - Overall

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral fractures - 2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% Cl)	0.95 [0.68, 1.32]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 No. People with new vertebral fractures - 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
3 Forearm BMD/C % 2 years from baseline	2	233	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-3.45, -0.35]
4 Forearm BMD/C% 4 years from baseline	2	268	Mean Difference (IV, Fixed, 95% CI)	-3.49 [-4.79, -2.20]
5 Total body BMD% from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	7.10 [1.06, 13.14]
6 Legs BMD % from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	6.5 [-0.87, 13.87]
7 Arms BMD % from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	9.0 [2.59, 15.41]
8 Femoral trochanter BMD % from baseline 4 years	1	191	Mean Difference (IV, Fixed, 95% CI)	15.61 [12.98, 18.24]
9 Pain mobility score- change from baseline	1	22	Mean Difference (IV, Fixed, 95% CI)	2.23 [0.59, 3.87]
10 Best available hip % from base- line 2 years	3	650	Mean Difference (IV, Fixed, 95% CI)	2.65 [1.93, 3.38]
11 Best available hip % from base- line 4 years	2	393	Mean Difference (IV, Fixed, 95% CI)	3.42 [2.62, 4.22]
12 Height % from baseline 4 years	2	194	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.10, 0.82]
13 Lumbar BMD % from baseline 2 years	7	907	Mean Difference (IV, Fixed, 95% CI)	10.38 [9.50, 11.25]
14 Lumbar BMD % from baseline 4 years	3	500	Mean Difference (IV, Fixed, 95% CI)	16.04 [14.61, 17.47]

Analysis 1.1. Comparison 1 Fluoride vs Placebo - Overall, Outcome 1 No. People with new vertebral fractures - 2 years.

Study or subgroup	Favours Fluoride	Favours Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Meunier 1998	69/208	37/146	- -	51.48%	1.45[0.91,2.3]
Pak 1995	6/54	16/56		12.66%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		33.79%	0.68[0.39,1.21]
Sebert 1995	2/35	1/41		2.07%	2.35[0.23,23.42]
Total (95% CI)	398	344	• • • • • • •	100%	0.95[0.68,1.32]
		Favours Fluoride	0.1 0.2 0.5 1 2 5 10 F	avours Placebo	

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Study or subgroup	Favours Fluoride	Favours Placebo		Peto Odds Ratio						Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	xed, 95	5% CI				Peto, Fixed, 95% CI
Total events: 110 (Favours Fluoride), 96 (Favours Placebo)										
Heterogeneity: Tau ² =0; Chi ² =9.82, c	df=3(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.7	4)										
			0.1	0.2	0.5	1	2	5	10	5 DI I	

Favours Fluoride 0.1 0.2 0.5 1 2 5 10 Favours Placebo

Analysis 1.2. Comparison 1 Fluoride vs Placebo - Overall, Outcome 2 No. People with new vertebral fractures - 4 years.

Study or subgroup	Favours Fluoride	Favours Placebo	Peto Odds Ratio				Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixe	ed, 95% CI			Peto, Fixed, 95% Cl
Hansson 1987	0/25	1/25	↓ +				1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38			•		19.74%	1.5[0.62,3.63]
Pak 1995	7/54	22/56					21.68%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	←	+			7.77%	0.21[0.05,0.87]
Riggs 1990	40/101	45/101					49.8%	0.82[0.47,1.43]
Total (95% CI)	326	320		•			100%	0.64[0.43,0.94]
Total events: 79 (Favours Fluoride), 97	(Favours Placebo)							
Heterogeneity: Tau ² =0; Chi ² =11.58, df=	4(P=0.02); I ² =65.47%							
Test for overall effect: Z=2.26(P=0.02)								
	Fa	avours Fluoride	0.1	0.2 0.5	1 2	5	¹⁰ Favours Placebo	

Analysis 1.3. Comparison 1 Fluoride vs Placebo - Overall, Outcome 3 Forearm BMD/C % 2 years from baseline.

Study or subgroup	Favou	rs Fluoride	Favours Placebo			Mean Difference				Weight M	lean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		F	ixed, 95% Cl				Fixed, 95% CI
Christiansen 1980	24	96.3 (7.3)	25	95.5 (7.5)			+			13.95%	0.8[-3.36,4.96]
Riggs 1990	93	97.3 (5.4)	91	99.6 (6.2)						86.05%	-2.34[-4.01,-0.67]
Total ***	117		116							100%	-1.9[-3.45,-0.35]
Heterogeneity: Tau ² =0; Chi ² =1.89, df	=1(P=0.17	7); I ² =47.02%									
Test for overall effect: Z=2.4(P=0.02)											
			Fav	ours Fluoride	-10	-5	0	5	10	Favours Placebo	

Analysis 1.4. Comparison 1 Fluoride vs Placebo - Overall, Outcome 4 Forearm BMD/C% 4 years from baseline.

Study or subgroup	Favou	rs Fluoride	Favours Placebo			Mean Difference				Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fix	ced, 95%	% CI			Fixed, 95% CI
Kleerekoper 1991	46	97.4 (5.1)	38	99.2 (4.2)						42.16%	-1.8[-3.8,0.2]
Riggs 1990	93	92.2 (5.3)	91	96.9 (6.4)						57.84%	-4.73[-6.44,-3.02]
Total ***	139		129			•				100%	-3.49[-4.79,-2.2]
Heterogeneity: Tau ² =0; Chi ² =4.78, df=	1(P=0.03	3); I ² =79.08%									
			Favo	ours Fluoride	-10	-5	0	5	10	Favours Placeb)

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Study or subgroup	Favo	ours Fluoride Favours Placebo				Ме	an Differen	ce		Weight Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed, 95% CI				Fixed, 95% CI
Test for overall effect: Z=5.28(P<0.000	01)				1	I.		1		
			Fa	ours Fluoride	-10	-5	0	5	10	Favours Placebo

Analysis 1.5. Comparison 1 Fluoride vs Placebo - Overall, Outcome 5 Total body BMD% from baseline.

Study or subgroup	Favou	rs Fluoride	Favours Placebo		Mean Difference				Weight	Mean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)		Fi	Fixed, 95% CI				Fixed, 95% CI
Gambacciani 1995	21	104.3 (10.8)	21	97.2 (9.1)				-	-	100%	7.1[1.06,13.14]
Total ***	21		21				_			100%	7.1[1.06,13.14]
Heterogeneity: Not applicable											
Test for overall effect: Z=2.3(P=0.02)											
			Fav	ours Fluoride	-10	-5	0	5	10	Favours Placebo	1

Analysis 1.6. Comparison 1 Fluoride vs Placebo - Overall, Outcome 6 Legs BMD % from baseline.

Study or subgroup	Favou	rs Fluoride	Favours Placebo Mea		Mean	Mean Difference			Weight I	lean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed, 95% CI					Fixed, 95% CI
Gambacciani 1995	21	103.7 (15.7)	21	97.2 (7.1)					•	100%	6.5[-0.87,13.87]
Total ***	21		21				-			100%	6.5[-0.87,13.87]
Heterogeneity: Not applicable											
Test for overall effect: Z=1.73(P=0.08)					1			1			
			Fav	ours Fluoride	-10	-5	0	5	10	Favours Placebo	

Analysis 1.7. Comparison 1 Fluoride vs Placebo - Overall, Outcome 7 Arms BMD % from baseline.

Study or subgroup	Favou	ırs Fluoride	Favours Placebo		Mean Difference				Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed, 95% CI				Fixed, 95% CI
Gambacciani 1995	21	105.5 (12.6)	21	96.5 (8.1)					100%	9[2.59,15.41]
Total ***	21		21				-		100%	9[2.59,15.41]
Heterogeneity: Not applicable										
Test for overall effect: Z=2.75(P=0.01)										
			Fav	ours Fluoride	-10	-5	0	5	¹⁰ Favours Placeb	0

Analysis 1.8. Comparison 1 Fluoride vs Placebo - Overall, Outcome 8 Femoral trochanter BMD % from baseline 4 years.

Study or subgroup	Favou	ırs Fluoride	uoride Favours Placebo				Mean	Differe	nce		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)			Fixe	d, 95%	СІ			Fixed, 95% CI
Riggs 1990	98	116.2 (11.1)	93	100.6 (7.2)							100%	15.61[12.98,18.24]
			Fav	ours Fluoride	-10	-5	i	0	5	10	Favours Placeb	0

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Study or subgroup	Favours Fluoride		Favours Placebo			Mean Difference				Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)		F	ixed, 95	% CI			Fixed, 95% CI
Total ***	98		93							100%	15.61[12.98,18.24]
Heterogeneity: Not applicable											
Test for overall effect: Z=11.62(P<0.0	001)										
			Fav	ours Fluoride	-10	-5	0	5	5 10	Favours Placeb	0

Analysis 1.9. Comparison 1 Fluoride vs Placebo - Overall, Outcome 9 Pain mobility score- change from baseline.

Study or subgroup	Favou	rs Fluoride	Favou	Favours Placebo		Mean Difference			Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fix	ed, 95% CI			Fixed, 95% CI
Grove 1981	12	2.8 (1.9)	10	0.6 (2)					100%	2.23[0.59,3.87]
Total ***	12		10				-		100%	2.23[0.59,3.87]
Heterogeneity: Not applicable										
Test for overall effect: Z=2.66(P=0.01)										
			Fav	ours Fluoride	-10	-5	0	5 10	Favours Placebo)

Analysis 1.10. Comparison 1 Fluoride vs Placebo - Overall, Outcome 10 Best available hip % from baseline 2 years.

Study or subgroup	Favou	rs Fluoride	Favours Placebo		Mean Difference					Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fix	ed, 95% C	l			Fixed, 95% CI
Meunier 1998	145	101.2 (22.9)	112	99.4 (18.5)						2.05%	1.8[-3.26,6.86]
Reginster 1998	100	102.5 (3)	100	100.8 (3)						76.09%	1.7[0.87,2.53]
Riggs 1990	99	105.5 (5.3)	94	99.5 (5.7)				-+		21.85%	6.05[4.5,7.6]
Total ***	344		306				•	•		100%	2.65[1.93,3.38]
Heterogeneity: Tau ² =0; Chi ² =23.56, d	f=2(P<0.0	0001); I ² =91.51%									
Test for overall effect: Z=7.17(P<0.00	01)										
			Fav	ours Fluoride	-10	-5	0	5	10	Favours Placebo	I

Analysis 1.11. Comparison 1 Fluoride vs Placebo - Overall, Outcome 11 Best available hip % from baseline 4 years.

Study or subgroup	Favou	rs Fluoride	Favou	rs Placebo		Me	an Difference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		F	ixed, 95% CI			Fixed, 95% CI
Reginster 1998	100	101.8 (3.1)	100	100.7 (3.6)					73.25%	1.1[0.17,2.03]
Riggs 1990	99	109.1 (5.5)	94	99.3 (5.4)				→	26.75%	9.78[8.24,11.32]
Total ***	199		194				•		100%	3.42[2.62,4.22]
Heterogeneity: Tau ² =0; Chi ² =89.28, d	f=1(P<0.0	0001); I ² =98.88%								
Test for overall effect: Z=8.41(P<0.00	01)									
			Fav	ours Fluoride	-10	-5	0	5 10	Favours Placeb	0

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Analysis 1.12. Comparison 1 Fluoride vs Placebo - Overall, Outcome 12 Height % from baseline 4 years.

Study or subgroup	Favou	rs Fluoride	Favours Placebo		Mean Difference			•		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixe	d, 95% CI				Fixed, 95% CI
Kleerekoper 1991	46	98.9 (1.4)	38	99.2 (2.5)			-			26.59%	-0.3[-1.19,0.59]
Pak 1995	54	99.6 (1.4)	56	99 (1.5)			+			73.41%	0.6[0.06,1.14]
Total ***	100		94				•			100%	0.36[-0.1,0.82]
Heterogeneity: Tau ² =0; Chi ² =2.85, df	=1(P=0.09	9); I ² =64.97%									
Test for overall effect: Z=1.53(P=0.13)										
			Fav	ours Fluoride	-10	-5	0	5	10	Favours Placebo)

Analysis 1.13. Comparison 1 Fluoride vs Placebo - Overall, Outcome 13 Lumbar BMD % from baseline 2 years.

Study or subgroup	Favou	ırs Fluoride	Favou	urs Placebo		Mean Di	fference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed,	95% CI		Fixed, 95% CI
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)			· · · · · · · · · · · · · · · · · · ·	- 7.35%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)				1.08%	12.2[3.78,20.62]
Meunier 1998	147	110.8 (21.2)	113	102.4 (14.9)			+	3.98%	8.4[4.01,12.79]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)				6.35%	9.34[5.86,12.82]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)			-	- 61.08%	8.04[6.92,9.16]
Riggs 1990	100	121 (8.5)	101	100.5 (6.2)				18.15%	20.54[18.48,22.6]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)				2.01%	11.06[4.88,17.24]
Total ***	466		441					▲ 100%	10.38[9.5,11.25]
Heterogeneity: Tau ² =0; Chi ² =118.24	, df=6(P<0	0.0001); I ² =94.93%	b						
Test for overall effect: Z=23.21(P<0.0	0001)					1		1	
			Fav	ours Fluoride	-10	-5 (0 5	¹⁰ Favours Plac	ebo

Analysis 1.14. Comparison 1 Fluoride vs Placebo - Overall, Outcome 14 Lumbar BMD % from baseline 4 years.

Study or subgroup	Favou	rs Fluoride	Favours Placebo		Mean Difference		Weight		Mean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)		Fi	xed, 95% CI			Fixed, 95% CI
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)				►	4.22%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					75.83%	10.4[8.76,12.04]
Riggs 1990	100	139.6 (15)	101	102.7 (6.5)				►	19.95%	36.91[33.71,40.11]
Total ***	248		252						100%	16.04[14.61,17.47]
Heterogeneity: Tau ² =0; Chi ² =209.7, d	=2(P<0.	0001); I ² =99.05%								
Test for overall effect: Z=22.01(P<0.00	01)									
			Fav	ours Fluoride	-10	-5	0	5 10	Favours Pl	acebo

Comparison 2. Side effects

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 GI Minor Overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 GI minor overall 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
3 GI minor overall 4 years	4	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [1.87, 5.39]
4 GI Minor Nausea	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.85]
5 GI Minor pain	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.36, 4.10]
6 GI Minor Dyspepsia	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.85]
7 GI major Overall	2	252	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.35, 2.28]

Analysis 2.1. Comparison 2 Side effects, Outcome 1 GI Minor Overall.

Study or subgroup	Favours Fluoride	Favours Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	← →	1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25	│ →	2.22%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		9.63%	2.64[1,6.97]
Meunier 1998	123/208	87/146	— <u>+</u> —	49.11%	0.98[0.64,1.51]
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		12.57%	2.56[1.09,6]
Sebert 1995	10/45	9/49	+	9.05%	1.27[0.46,3.45]
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Favours Fluoride), 1	20 (Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df=	8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
	F	avours Fluoride	0.1 0.2 0.5 1 2 5 10 F	avours Placebo	

Analysis 2.2. Comparison 2 Side effects, Outcome 2 GI minor overall 2 years.

Study or subgroup	Favours Fluoride	Favours Placebo		Peto Odds Ratio						Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	ixed, 9	5% CI				Peto, Fixed, 95% Cl
Gambacciani 1995	7/30	6/30				+				9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	←						→	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146			-	-				75.07%	0.98[0.64,1.51]
Sebert 1995	10/45	9/49				+				13.83%	1.27[0.46,3.45]
Total (95% CI)	297	239			-	•				100%	1.04[0.71,1.51]
Total events: 141 (Favours Fluoride	e), 103 (Favours Placebo)										
	F	avours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

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Study or subgroup	Favours Fluoride	Favours Placebo		Peto Odds Ratio				Weight	Peto Odds Ratio		
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
Heterogeneity: Tau ² =0; Chi ² =0.28, df=3	(P=0.96); I ² =0%										
Test for overall effect: Z=0.19(P=0.85)											
		Favours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

Analysis 2.3. Comparison 2 Side effects, Outcome 3 GI minor overall 4 years.

Study or subgroup	Favours Fluoride	Favours Placebo		Peto Odds Ratio			Weight	Peto Odds Ratio			
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Kleerekoper 1991	16/46	6/38				_	-		-	29.76%	2.64[1,6.97]
Pak 1995	5/54	4/56				+				15.23%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102							\rightarrow	16.17%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101				-	-			38.84%	2.56[1.09,6]
Total (95% CI)	262	297								100%	3.17[1.87,5.39]
Total events: 48 (Favours Fluoride), 1	7 (Favours Placebo)										
Heterogeneity: Tau ² =0; Chi ² =8.18, df	=3(P=0.04); I ² =63.33%										
Test for overall effect: Z=4.27(P<0.00	01)										
		Favours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

Analysis 2.4. Comparison 2 Side effects, Outcome 4 GI Minor Nausea.

Study or subgroup	Favours Fluoride	Favours Placebo		P	eto Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N		Pet	o, Fixed	, 95% CI				Peto, Fixed, 95% Cl
Grove 1981	1/14	1/14	←					→	100%	1[0.06,16.85]
Total (95% CI)	14	14							100%	1[0.06,16.85]
Total events: 1 (Favours Fluoride), 1 (F	avours Placebo)									
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
		Favours Fluoride	0.1	0.2 0	.5 1	2	5	10	Favours Placebo	

Analysis 2.5. Comparison 2 Side effects, Outcome 5 GI Minor pain.

Study or subgroup	Favours Fluoride	Favours Placebo			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Gambacciani 1995	7/30	6/30				-				100%	1.21[0.36,4.1]
Total (95% CI)	30	30						-		100%	1.21[0.36,4.1]
Total events: 7 (Favours Fluoride), 6 (F	avours Placebo)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.31(P=0.76)											
		Favours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

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Analysis 2.6. Comparison 2 Side effects, Outcome 6 GI Minor Dyspepsia.

Study or subgroup	Favours Fluoride	Favours Placebo			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Grove 1981	1/14	1/14	←			+			\rightarrow	100%	1[0.06,16.85]
Total (95% CI)	14	14	_							100%	1[0.06,16.85]
Total events: 1 (Favours Fluoride), 1 (Fa	avours Placebo)										
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
		Favours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

Analysis 2.7. Comparison 2 Side effects, Outcome 7 GI major Overall.

Study or subgroup	Favours Fluoride	Favours Placebo			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Hansson 1987	0/25	1/25	+						-	5.72%	0.14[0,6.82]
Riggs 1990	9/101	9/101				+				94.28%	1[0.38,2.63]
Total (95% CI)	126	126								100%	0.89[0.35,2.28]
Total events: 9 (Favours Fluoride),	, 10 (Favours Placebo)										
Heterogeneity: Tau ² =0; Chi ² =0.94,	df=1(P=0.33); I ² =0%										
Test for overall effect: Z=0.24(P=0.	.81)				1						
		Favours Fluoride	0.1	0.2	0.5	1	2	5	10	Favours Placebo	

Favours Fluoride Favours Placebo

Comparison 3. Number of patients with new nonvertebral fractures

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Nonvertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
2 Pelvis 4 years	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.69 [1.15, 19.09]
3 Proximal Femur 4 years	1	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.73 [0.95, 7.79]
4 Hip 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.27, 7.16]
5 Foot 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.03, 3.49]
6 Tibia 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.48 [0.10, 293.94]
7 Humerus 4 years	3	422	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [0.51, 9.51]
8 Wrist 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.23, 3.34]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
9 Rib 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.18, 6.31]
10 Fissures or mi- crofractures	4	608	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [2.31, 9.05]
11 Bone spurs	1	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.17, 3.35]
12 Traumatic fractures	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.06, 16.81]
13 Non vertebral frac- ture overall 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
14 Non vertebral frac- ture overall 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
15 Rib 4 years	3	512	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.57, 3.11]
16 Hip 4 years	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.05, 5.00]
17 Wrist 4 years	3	512	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.35, 2.90]
18 Foot 4 years	3	512	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.19 [0.81, 5.98]
19 Tibia 4 years	1	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.30 [2.59, 26.57]

Analysis 3.1. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 1 Nonvertebral fractures overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Kleerekoper 1991	13/46	7/38		11.61%	1.71[0.63,4.66]
Meunier 1998	29/208	17/146		29.56%	1.22[0.65,2.3]
Pak 1995	3/54	5/56	+	5.69%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100		15.54%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101		37.6%	4.46[2.56,7.79]
Total (95% CI)	509	441	•	100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =14.84, o	df=4(P=0.01); I ² =73.05%	b			
Test for overall effect: Z=3.85(P=0)					
			0.1 0.2 0.5 1 2 5 10		

Analysis 3.2. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 2 Pelvis 4 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% Cl							Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
Pak 1995	1/54	0/56		1					-+	12.83%	7.67[0.15,386.69]
			0.1 C	0.2	0.5	1	2	5	10		

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Riggs 1990	6/101	1/101		87.17%	4.36[0.97,19.62]
Total (95% CI)	155	157		100%	4.69[1.15,19.09]
Total events: 7 (Treatment), 1 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.07,	df=1(P=0.79); I ² =0%				
Test for overall effect: Z=2.16(P=0.	03)				
		0.	0.1 0.2 0.5 1 2 5 10		

Analysis 3.3. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 3 Proximal Femur 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Riggs 1990	11/101	4/101		100%	2.73[0.95,7.79]
Total (95% CI)	101	101		100%	2.73[0.95,7.79]
Total events: 11 (Treatment), 4 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.87(P=0.06)					
			0.1 0.2 0.5 1 2 5 10		

Analysis 3.4. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 4 Hip 2 years.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	Fixed,	95% CI				Peto, Fixed, 95% Cl
Meunier 1998	4/208	2/146		-					-	100%	1.39[0.27,7.16]
Total (95% CI)	208	146		-					-	100%	1.39[0.27,7.16]
Total events: 4 (Treatment), 2 (Control)	1										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.4(P=0.69)											
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.5. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 5 Foot 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio						Weight	Peto Odds Ratio	
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
Meunier 1998	1/208	2/146	•		1			-		100%	0.35[0.03,3.49]
Total (95% CI)	208	146								100%	0.35[0.03,3.49]
Total events: 1 (Treatment), 2 (Control)											
Heterogeneity: Not applicable											
Test for overall effect: Z=0.9(P=0.37)											
			0.1	0.2	0.5	1	2	5	10		

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Analysis 3.6. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 6 Tibia 2 years.

Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Meunier 1998	1/208	0/146						-		100%	5.48[0.1,293.94]
Total (95% CI)	208	146								100%	5.48[0.1,293.94]
Total events: 1 (Treatment), 0 (Control))										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.84(P=0.4)											
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.7. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 7 Humerus 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio				Weight	Peto Odds Ratio	
	n/N	n/N		Peto, Fix	ced, 95% CI			Peto, Fixed, 95% Cl	
Pak 1995	0/54	1/56					13.92%	0.14[0,7.07]	
Reginster 1998	0/10	1/100	◀──	+			4.6%	0.33[0,304.22]	
Riggs 1990	5/101	1/101		-	-		81.48%	3.92[0.78,19.84]	
Total (95% CI)	165	257					100%	2.2[0.51,9.51]	
Total events: 5 (Treatment), 3 (Contr	rol)								
Heterogeneity: Tau ² =0; Chi ² =2.68, df	=2(P=0.26); I ² =25.34%								
Test for overall effect: Z=1.06(P=0.29)								
			01 02	0.5	1 2	5 10			

Analysis 3.8. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 8 Wrist 2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N	P	eto, Fixed, 95% CI			Peto, Fixed, 95% Cl
Meunier 1998	5/208	4/146				100%	0.87[0.23,3.34]
Total (95% CI)	208	146				100%	0.87[0.23,3.34]
Total events: 5 (Treatment), 4 (Control)	1						
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.84)							
			01 02	05 1 2	5 10		

Analysis 3.9. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 9 Rib 2 years.

Study or subgroup	Treatment	Control		Peto O	dds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fi	xed, 9	95% CI				Peto, Fixed, 95% CI
Meunier 1998	3/208	2/146							100%	1.05[0.18,6.31]
Total (95% CI)	208	146							100%	1.05[0.18,6.31]
		0.	.1 0.2	0.5	1	2	5	10		

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Study or subgroup	Treatment n/N	Control n/N			Peto Peto, F	Odds ixed,	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
Total events: 3 (Treatment), 2 (Contro	ι)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.06(P=0.95)											
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.10. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 10 Fissures or microfractures.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Pak 1995	0/54	0/56			Not estimable
Riggs 1982	26/101	2/101		73.44%	7.24[3.27,16.06]
Riggs 1990	3/101	4/101		20.58%	0.74[0.17,3.35]
Sebert 1995	2/45	0/49		5.98%	8.26[0.51,134.42]
Total (95% CI)	301	307		100%	4.57[2.31,9.05]
Total events: 31 (Treatment), 6 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =7.05, d	f=2(P=0.03); I ² =71.62%				
Test for overall effect: Z=4.37(P<0.00	001)				
			0.1 0.2 0.5 1 2 5 10		

Analysis 3.11. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 11 Bone spurs.

Study or subgroup	Treatment	Control		Peto Odds Ratio						Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Riggs 1990	3/101	4/101						-		100%	0.74[0.17,3.35]
Total (95% CI)	101	101								100%	0.74[0.17,3.35]
Total events: 3 (Treatment), 4 (Control)											
Heterogeneity: Not applicable											
Test for overall effect: Z=0.38(P=0.7)											
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.12. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 12 Traumatic fractures.

Study or subgroup	Treatment n/N	Control n/N		Pe Pet	eto Odds o, Fixed,	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pak 1995	1/54	1/56	•					•	100%	1.04[0.06,16.81]
Total (95% CI)	54	56							100%	1.04[0.06,16.81]
Total events: 1 (Treatment), 1 (Control)										
Heterogeneity: Not applicable										
Test for overall effect: Z=0.03(P=0.98)										
			0.1	0.2 0.	5 1	2	5	10		

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Analysis 3.13. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 13 Non vertebral fracture overall 2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio						Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Meunier 1998	29/208	17/146			-	-+				100%	1.22[0.65,2.3]
Total (95% CI)	208	146			-					100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Cont	rol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.63(P=0.53)											
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.14. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 14 Non vertebral fracture overall 4 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio						Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Kleerekoper 1991	13/46	7/38			-		•			16.49%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	-		•					8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100								22.07%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101					_	-	_	53.37%	4.46[2.56,7.79]
Total (95% CI)	301	295					\bullet	•		100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =11.81, o	df=3(P=0.01); I ² =74.59%										
Test for overall effect: Z=4.18(P<0.00	001)										
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.15. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 15 Rib 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio							Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	xed, 95	% CI				Peto, Fixed, 95% CI
Pak 1995	0/54	1/56	◀	+					-	4.7%	0.14[0,7.07]
Reginster 1998	2/100	1/100					+		\rightarrow	13.96%	1.96[0.2,19.07]
Riggs 1990	11/101	8/101				+		-		81.34%	1.41[0.55,3.63]
Total (95% CI)	255	257								100%	1.33[0.57,3.11]
Total events: 13 (Treatment), 10 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =1.39, d	lf=2(P=0.5); l ² =0%										
Test for overall effect: Z=0.65(P=0.5	1)										
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.16. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 16 Hip 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio							Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
Pak 1995	0/54	1/56	•							33.44%	0.14[0,7.07]
Reginster 1998	1/100	1/100	←			-			→	66.56%	1[0.06,16.1]
Total (95% CI)	154	156								100%	0.52[0.05,5]
Total events: 1 (Treatment), 2 (Contr	ol)										
Heterogeneity: Tau ² =0; Chi ² =0.64, df	=1(P=0.42); I ² =0%										
Test for overall effect: Z=0.57(P=0.57)										
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.17. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 17 Wrist 4 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI			Peto, Fixed, 95% CI
Pak 1995	1/54	0/56			+	7.34%	7.67[0.15,386.69]
Reginster 1998	5/100	3/100				56.68%	1.68[0.41,6.88]
Riggs 1990	1/101	4/101	◀──	•		35.98%	0.29[0.05,1.73]
Total (95% CI)	255	257				100%	1[0.35,2.9]
Total events: 7 (Treatment), 7 (Con	trol)						
Heterogeneity: Tau ² =0; Chi ² =3.39, d	lf=2(P=0.18); I ² =41.03%						
Test for overall effect: Z=0(P=1)							
			0.1 0.2	0.5 1 2	5 10		

Analysis 3.18. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 18 Foot 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio						Weight	Peto Odds Ratio	
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Pak 1995	0/54	1/56	+							6.53%	0.14[0,7.07]
Reginster 1998	2/100	1/100					•		→	19.39%	1.96[0.2,19.07]
Riggs 1990	9/101	3/101				+	-			74.08%	2.88[0.9,9.22]
Total (95% CI)	255	257				-				100%	2.19[0.81,5.98]
Total events: 11 (Treatment), 5 (Con	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =2.11, d	lf=2(P=0.35); I ² =5.19%										
Test for overall effect: Z=1.54(P=0.1	2)										
			0.1	0.2	0.5	1	2	5	10		

Analysis 3.19. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 19 Tibia 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio							Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI							Peto, Fixed, 95% Cl
Riggs 1990	12/101	0/101					_			100%	8.3[2.59,26.57]
			0.1	0.2	0.5	1	2	5	10		

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Comparison 4. Musculoskeletal pain

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Lower limb pain 2 years	2	448	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.20 [1.77, 5.78]
2 Lower limb pain 4 years	4	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.00 [2.57, 6.22]
3 Finger paresthesia	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]

Analysis 4.1. Comparison 4 Musculoskeletal pain, Outcome 1 Lower limb pain 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Meunier 1998	37/208	7/146	——————————————————————————————————————	85.14%	3.29[1.73,6.24]
Sebert 1995	5/45	2/49		14.86%	2.74[0.59,12.71]
Total (95% CI)	253	195		100%	3.2[1.77,5.78]
Total events: 42 (Treatment), 9 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.05, df	=1(P=0.83); I ² =0%				
Test for overall effect: Z=3.86(P=0)					
			0.1 0.2 0.5 1 2 5 10		

Analysis 4.2. Comparison 4 Musculoskeletal pain, Outcome 2 Lower limb pain 4 years.

Study or subgroup	Treatment	Control	Peto Od	ds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% Cl
Kleerekoper 1991	23/46	13/38	_		26.3%	1.89[0.8,4.48]
Pak 1995	6/54	8/56	+		15.71%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		\rightarrow	15.37%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101			42.62%	6.78[3.44,13.36]
Total (95% CI)	262	297		-	100%	4[2.57,6.22]
Total events: 80 (Treatment), 26 (Co	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =20.77,	df=3(P=0); I ² =85.56%					
Test for overall effect: Z=6.14(P<0.00	001)					
			0.1 0.2 0.5	1 2 5 10		

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Analysis 4.3. Comparison 4 Musculoskeletal pain, Outcome 3 Finger paresthesia.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
Grove 1981	0/14	1/14	4						-	100%	0.14[0,6.82]
Total (95% CI)	14	14								100%	0.14[0,6.82]
Total events: 0 (Treatment), 1 (Control)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1(P=0.32)											
			0.1	0.2	0.5	1	2	5	10		

Comparison 5. Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
2 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
3 Withdrawals and dropouts 4 years	4	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.69, 1.47]

Analysis 5.1. Comparison 5 Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control		Peto Od	lds Ratio	Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% CI
Christiansen 1980	3/27	3/28	_		+	- 3.41%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30			•	8.02%	1[0.33,2.99]
Grove 1981	2/14	4/14	◀──	+		3.06%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	◀──	-+		2.35%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38		+-		10.49%	0.72[0.27,1.86]
Pak 1995	6/54	5/56			+	6.25%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100			—	29.93%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101		·	-	28.17%	1.14[0.64,2.05]
Sebert 1995	9/35	8/41			+	8.32%	1.42[0.49,4.17]
Total (95% CI)	432	433				100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (Control)							
Heterogeneity: Tau ² =0; Chi ² =3.17, df	=8(P=0.92); I ² =0%						
Test for overall effect: Z=0.17(P=0.86))						
	Fa	avours Treatment	0.1 0.2	0.5	1 2 5	^{5 10} Favours Control	

Analysis 5.2. Comparison 5 Withdrawals and dropouts, Outcome 2 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control		Peto Odds	Ratio		Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed,	95% CI			Peto, Fixed, 95% CI
Christiansen 1980	3/27	3/28	-	+		_	14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30					35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	◀—	•			13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41			•		36.48%	1.42[0.49,4.17]
Total (95% CI)	106	113		-			100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ontrol)							
Heterogeneity: Tau ² =0; Chi ² =1.23, d	f=3(P=0.75); I ² =0%							
Test for overall effect: Z=0.07(P=0.94	4)							
	Fay	vours Treatment	0.1 0.	2 0.5 1	2	5 10	Favours Control	

Analysis 5.3. Comparison 5 Withdrawals and dropouts, Outcome 3 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, s	95% CI				Peto, Fixed, 95% Cl
Hansson 1987	1/25	3/25	←		+					3.52%	0.34[0.05,2.61]
Pak 1995	6/54	5/56				+		_		9.37%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100				-	-			44.87%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101			-	-				42.23%	1.14[0.64,2.05]
Total (95% CI)	280	282				\blacklozenge				100%	1[0.69,1.47]
Total events: 80 (Treatment), 80 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =1.49, d	f=3(P=0.68); I ² =0%										
Test for overall effect: Z=0.02(P=0.98	3)							1			
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Comparison 6. Subgroup Analysis: Type of Fluoride

Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral frac- tures-2 years	4	1033	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.72, 1.28]
1.1 NaF	3	531	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.60, 1.28]
1.2 MFP	2	502	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.70, 1.68]
2 No. People with new vertebral frac- tures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.55, 1.20]
2.1 NaF	4	446	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.46, 1.05]
2.2 MFP	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.73 [1.15, 19.41]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
3 Lumbar BMD % 2 years from baseline	7	1094	Mean Difference (IV, Fixed, 95% CI)	8.95 [8.18, 9.72]
3.1 NaF	4	533	Mean Difference (IV, Fixed, 95% CI)	10.48 [9.24, 11.71]
3.2 MFP	4	561	Mean Difference (IV, Fixed, 95% CI)	7.99 [7.01, 8.97]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 NaF	2	301	Mean Difference (IV, Fixed, 95% CI)	34.57 [31.13, 38.01]
4.2 MFP	1	200	Mean Difference (IV, Fixed, 95% CI)	10.40 [8.76, 12.04]
5 GI minor overall	9	1291	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.11, 1.92]
5.1 NaF	7	856	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [1.38, 2.94]
5.2 MFP	3	435	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.67, 1.51]
6 GI minor 2 years	4	682	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.74, 1.43]
6.1 NaF	2	247	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.62, 1.90]
6.2 MFP	3	435	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.67, 1.51]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 NaF	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.2 MFP	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Non vertebral frac- tures overall	5	1096	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.35, 2.60]
8.1 NaF	4	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.42 [1.61, 3.63]
8.2 MFP	2	481	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.69, 2.04]
9 Non vertebral frac- tures 2 years	1	500	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.72, 2.11]
9.1 NaF	1	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.52, 2.83]
9.2 MFP	1	281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.62, 2.50]
10 Non vertebral fractures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 NaF	3	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.96 [1.87, 4.70]
10.2 MFP	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.46, 2.62]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
11 Lower limb pain syndrome	6	1153	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.97 [2.81, 5.61]
11.1 NaF	5	778	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.19 [2.81, 6.26]
11.2 MFP	2	375	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.41 [1.73, 6.72]
12 Withdrawals and dropouts overall	8	805	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.70, 1.34]
12.1 NaF	6	529	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.62, 1.44]
12.2 MFP	2	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.61, 1.67]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 NaF	2	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.20, 2.35]
13.2 MFP	2	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.56, 2.58]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 NaF	4	446	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.63, 1.54]
14.2 MFP	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.52, 1.62]

Analysis 6.1. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
6.1.1 NaF					
Meunier 1998	27/73	37/146		21.94%	1.75[0.95,3.24]
Pak 1995	6/54	16/56		9.63%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		25.7%	0.68[0.39,1.21]
Subtotal (95% CI)	228	303	-	57.26%	0.87[0.6,1.28]
Total events: 66 (Treatment), 95 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =9.58, df	=2(P=0.01); I ² =79.11%				
Test for overall effect: Z=0.71(P=0.48)	1				
6.1.2 MFP					
Meunier 1998	19/67	37/146		19.4%	1.17[0.61,2.25]
Sebert 1995	21/102	38/187	+	23.34%	1.02[0.56,1.85]
Subtotal (95% CI)	169	333		42.74%	1.08[0.7,1.68]
Total events: 40 (Treatment), 75 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.09, df	=1(P=0.76); I ² =0%				
Test for overall effect: Z=0.35(P=0.73))				
			0.1 0.2 0.5 1 2 5	10	

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Analysis 6.2. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
6.2.1 NaF					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Riggs 1990	40/101	45/101		49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	226	220		92.23%	0.7[0.46,1.05]
Total events: 78 (Treatment), 90 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.05, df=3	B(P=0.03); I ² =66.84%				
Test for overall effect: Z=1.73(P=0.08)					
6.2.2 MFP					
Reginster 1998	7/100	1/100		7.77%	4.73[1.15,19.41]
Subtotal (95% CI)	100	100		7.77%	4.73[1.15,19.41]
Total events: 7 (Treatment), 1 (Contro	ι)				
Heterogeneity: Not applicable					
Test for overall effect: Z=2.16(P=0.03)					
Total (95% CI)	326	320	-	100%	0.81[0.55,1.2]
Total events: 85 (Treatment), 91 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =15.57, df=	=4(P=0); I ² =74.32%				
Test for overall effect: Z=1.06(P=0.29)					
Test for subgroup differences: Chi ² =6.5	53, df=1 (P=0.01), I ² =84	4.68%			
			0.1 0.2 0.5 1 2 5	10	

Analysis 6.3.	Comparison 6	Subgroup Anal	vsis: Type of	Fluoride. Outcome	B Lumbar BMD % 2	vears from baseline.

Study or subgroup	Tre	eatment	Control		Mean Difference			Weight	Mean Difference	
	N	Mean(SD)	Ν	Mean(SD)			Fixed, 95% CI			Fixed, 95% CI
6.3.1 NaF										
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)					0.83%	12.2[3.78,20.62]
Meunier 1998	73	109.3 (5.8)	113	102.4 (4.3)					24.56%	6.9[5.35,8.45]
Pak 1995	48	109.3 (10.3)	51	100.3 (6.9)					4.87%	8.98[5.5,12.46]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)				•	8.28%	21.79[19.12,24.46]
Subtotal ***	246		287					•	38.54%	10.48[9.24,11.71]
Heterogeneity: Tau ² =0; Chi ² =90	.5, df=3(P<0.0	001); I ² =96.69%								
					-10	-5	0	5 10		

Fluoride for treating postmenopausal osteoporosis (Review)

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Study or subgroup	Treatment		c	Control		Mean Differe	ence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	D) Fixed, 9		CI		Fixed, 95% CI
Test for overall effect: Z=16.61(P<0.00	01)								
6.3.2 MFP									
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)			+	5.64%	6.2[2.97,9.43]
Meunier 1998	147	110.8 (14.5)	113	102.4 (8.5)			→	7.41%	8.4[5.58,11.22]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)				46.87%	8.04[6.92,9.16]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)			>	1.54%	11.06[4.88,17.24]
Subtotal ***	294		267				•	61.46%	7.99[7.01,8.97]
Heterogeneity: Tau ² =0; Chi ² =2.21, df=	3(P=0.53	3); I ² =0%							
Test for overall effect: Z=16(P<0.0001)									
Total ***	540		554				•	100%	8.95[8.18,9.72]
Heterogeneity: Tau ² =0; Chi ² =102.27, c	f=7(P<0	.0001); I ² =93.16%							
Test for overall effect: Z=22.85(P<0.00	01)								
Test for subgroup differences: Chi ² =9.	55, df=1	(P=0), I ² =89.53%							
					-10	-5 0	5 10		

Analysis 6.4. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Treatment		с	ontrol		Mean D	ifference	Weight		Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed,	, 95% CI			Fixed, 95% CI
6.4.1 NaF										
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)					4.53%	18.68[11.73,25.63]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)					13.96%	39.73[35.77,43.69]
Subtotal ***	149		152						18.5%	34.57[31.13,38.01]
Heterogeneity: Tau ² =0; Chi ² =26.58, df	=1(P<0.0	0001); I ² =96.24%								
Test for overall effect: Z=19.68(P<0.00	01)									
6.4.2 MFP										
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					81.5%	10.4[8.76,12.04]
Subtotal ***	100		100					◄	81.5%	10.4[8.76,12.04]
Heterogeneity: Not applicable										
Test for overall effect: Z=12.43(P<0.00	01)									
Total ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, c	lf=2(P<0	.0001); l ² =98.89%								
Test for overall effect: Z=19.69(P<0.00	01)									
Test for subgroup differences: Chi ² =15	54.33, df	=1 (P<0.0001), I ² =9	99.35%							
					-10	-5	0 5	10		

Analysis 6.5. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio		
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI		
6.5.1 NaF							
Grove 1981	1/14	1/14	← →	0.96%	1[0.06,16.85]		
Hansson 1987	4/25	0/25		1.87%	8.42[1.11,63.64]		
			0.1 0.2 0.5 1 2 5 10				

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Kleerekoper 1991	16/46	6/38	+	8.1%	2.64[1,6.97]
Meunier 1998	45/73	87/146		23.28%	1.09[0.61,1.93]
Pak 1995	5/54	4/56		4.14%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		4.4%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		10.57%	2.56[1.09,6]
Subtotal (95% CI)	374	482	•	53.31%	2.02[1.38,2.94]
Total events: 98 (Treatment), 105 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =17.58, df	=6(P=0.01); I ² =65.88%	6			
Test for overall effect: Z=3.63(P=0)					
6.5.2 MFP					
Gambacciani 1995	7/30	6/30	+	5.15%	1.21[0.36,4.1]
Meunier 1998	78/135	87/146	_	33.93%	0.93[0.58,1.49]
Sebert 1995	10/45	9/49	+	7.6%	1.27[0.46,3.45]
Subtotal (95% CI)	210	225	•	46.69%	1.01[0.67,1.51]
Total events: 95 (Treatment), 102 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.4, df=2	(P=0.82); I ² =0%				
Test for overall effect: Z=0.03(P=0.98)					
Total (95% CI)	584	707	•	100%	1.46[1.11,1.92]
Total events: 193 (Treatment), 207 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =24.04, df	=9(P=0); I ² =62.56%				
Test for overall effect: Z=2.67(P=0.01)					
Test for subgroup differences: Chi ² =6.	05, df=1 (P=0.01), l ² =8	83.47%			
		0.1	0.2 0.5 1 2 5 1	0	

Analysis 6.6. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
6.6.1 NaF					
Grove 1981	1/14	1/14	← →	1.35%	1[0.06,16.85]
Meunier 1998	45/73	87/146	_ -	32.82%	1.09[0.61,1.93]
Subtotal (95% CI)	87	160		34.17%	1.09[0.62,1.9]
Total events: 46 (Treatment), 88 (Cont	trol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.95); I ² =0%				
Test for overall effect: Z=0.29(P=0.77)					
6.6.2 MFP					
Gambacciani 1995	7/30	6/30	+	7.26%	1.21[0.36,4.1]
Meunier 1998	78/135	87/146	— <u>—</u>	47.84%	0.93[0.58,1.49]
Sebert 1995	10/45	9/49		10.72%	1.27[0.46,3.45]
Subtotal (95% CI)	210	225	•	65.83%	1.01[0.67,1.51]
Total events: 95 (Treatment), 102 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.4, df=2	(P=0.82); I ² =0%				
Test for overall effect: Z=0.03(P=0.98)					
Total (95% CI)	297	385		100%	1.03[0.74,1.43]
Total events: 141 (Treatment), 190 (Co	ontrol)				
			0.1 0.2 0.5 1 2 5 10		

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Study or subgroup	Treatment n/N	Control n/N			Peto Peto, F	Odds ixed,	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
Heterogeneity: Tau ² =0; Chi ² =0.45, d	f=4(P=0.98); I ² =0%										
Test for overall effect: Z=0.19(P=0.8	5)										
Test for subgroup differences: Chi ² =	=0.05, df=1 (P=0.83), I ² =0	9%									
			0.1	0.2	0.5	1	2	5	10		

Analysis 6.7. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
6.7.1 NaF					
Hansson 1987	4/25	0/25	│───	6.42%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		36.35%	2.56[1.09,6]
Subtotal (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
6.7.2 MFP					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
Test for subgroup differences: Not appl	licable				
		0.1	0.2 0.5 1 2 5 10)	

Analysis 6.8. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
6.8.1 NaF					
Kleerekoper 1991	13/46	7/38		10.52%	1.71[0.63,4.66]
Meunier 1998	10/73	17/146	+	14.55%	1.21[0.52,2.83]
Pak 1995	3/54	5/56		5.15%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101	— —	34.05%	4.46[2.56,7.79]
Subtotal (95% CI)	274	341	•	64.27%	2.42[1.61,3.63]
Total events: 87 (Treatment), 53 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =11.2, df	f=3(P=0.01); I ² =73.22%				
Test for overall effect: Z=4.27(P<0.00	001)				
			0.1 0.2 0.5 1 2 5 10		

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	_				_							
Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds	Ratio
	n/N	n/N			Peto, F	Fixed,	95% CI				Peto, Fixed,	95% CI
6.8.2 MFP												
Meunier 1998	19/135	17/146			_	+				21.65%	1.24	4[0.62,2.5]
Reginster 1998	12/100	11/100				•				14.08%	1.1[0.46,2.62]
Subtotal (95% CI)	235	246								35.73%	1.19[0	.69,2.04]
Total events: 31 (Treatment), 28 (Co	ntrol)											
Heterogeneity: Tau ² =0; Chi ² =0.04, d	f=1(P=0.83); I ² =0%											
Test for overall effect: Z=0.61(P=0.54	1)											
Total (95% CI)	509	587					•			100%	1.87	[1.35,2.6]
Total events: 118 (Treatment), 81 (C	ontrol)											
Heterogeneity: Tau ² =0; Chi ² =15.49,	df=5(P=0.01); I ² =67.72%											
Test for overall effect: Z=3.79(P=0)												
Test for subgroup differences: Chi ² =	4.24, df=1 (P=0.04), I ² =76.4	4%										
			0.1	0.2	0.5	1	2	5	10			

Analysis 6.9. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
6.9.1 NaF					
Meunier 1998	10/73	17/146		40.19%	1.21[0.52,2.83]
Subtotal (95% CI)	73	146		40.19%	1.21[0.52,2.83]
Total events: 10 (Treatment), 17 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
6.9.2 MFP					
Meunier 1998	19/135	17/146		59.81%	1.24[0.62,2.5]
Subtotal (95% CI)	135	146		59.81%	1.24[0.62,2.5]
Total events: 19 (Treatment), 17 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
Total (95% CI)	208	292		100%	1.23[0.72,2.11]
Total events: 29 (Treatment), 34 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=	=0.96); l ² =0%				
Test for overall effect: Z=0.75(P=0.46)					
Test for subgroup differences: Chi ² =0, o	df=1 (P=0.96), I ² =0%				
		0.1	02 05 1 2 5	10	

Analysis 6.10. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% Cl	Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
6.10.1 NaF					
Kleerekoper 1991	13/46	7/38		16.49%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	· · · · · · · · · · · ·	8.07%	0.61[0.15,2.55]
			0.1 0.2 0.5 1 2 5 10)	

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Study or subgroup	dy or subgroup Treatment Co		Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Riggs 1990	61/101	24/101		53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	201	195	-	77.93%	2.96[1.87,4.7]
Total events: 77 (Treatment), 36 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =7.91, df=2	2(P=0.02); I ² =74.72%				
Test for overall effect: Z=4.62(P<0.000)	1)				
6.10.2 MFP					
Reginster 1998	12/100	11/100		22.07%	1.1[0.46,2.62]
Subtotal (95% CI)	100	100		22.07%	1.1[0.46,2.62]
Total events: 12 (Treatment), 11 (Cont	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.83)					
Total (95% CI)	301	295	•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.81, df	=3(P=0.01); I ² =74.59%				
Test for overall effect: Z=4.18(P<0.000)	1)				
Test for subgroup differences: Chi ² =3.	9, df=1 (P=0.05), I ² =74.3	3%			
			0.1 0.2 0.5 1 2	5 10	

Analysis 6.11. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
6.11.1 NaF					
Kleerekoper 1991	23/46	13/38	+ +	16.02%	1.89[0.8,4.48]
Meunier 1998	14/73	7/146		13.16%	5.21[2.01,13.51]
Pak 1995	6/54	8/56		9.57%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.37%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101	· · · · · · · · · · · · · · · · · · ·	25.96%	6.78[3.44,13.36]
Subtotal (95% CI)	335	443	•	74.08%	4.19[2.81,6.26]
Total events: 94 (Treatment), 33 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =21.02, df=	=4(P=0); I ² =80.97%				
Test for overall effect: Z=7(P<0.0001)					
6.11.2 MFP					
Meunier 1998	23/135	7/146		20.85%	3.59[1.69,7.66]
Sebert 1995	5/45	2/49		5.08%	2.74[0.59,12.71]
Subtotal (95% CI)	180	195		25.92%	3.41[1.73,6.72]
Total events: 28 (Treatment), 9 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.1, df=1(P=0.76); I ² =0%				
Test for overall effect: Z=3.54(P=0)					
Total (95% CI)	515	638	•	100%	3.97[2.81,5.61]
Total events: 122 (Treatment), 42 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =21.38, df=	=6(P=0); I ² =71.93%				
Test for overall effect: Z=7.83(P<0.0001	L)				
Test for subgroup differences: Chi ² =0.2	26, df=1 (P=0.61), I ² =	0%			
		0.1	0.2 0.5 1 2 5 10		

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Analysis 6.12. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 12 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
6.12.1 NaF					
Christiansen 1980	3/27	3/28		3.7%	1.04[0.19,5.59]
Grove 1981	2/14	4/14	┥───	3.33%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	+	2.56%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	11.4%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		6.8%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101	_	30.63%	1.14[0.64,2.05]
Subtotal (95% CI)	267	262	-	58.41%	0.94[0.62,1.44]
Total events: 79 (Treatment), 76 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =2.63, df=5	6(P=0.76); I ² =0%				
Test for overall effect: Z=0.27(P=0.79)					
6.12.2 MFP					
Reginster 1998	38/100	40/100		32.54%	0.92[0.52,1.62]
Sebert 1995	9/35	8/41		9.04%	1.42[0.49,4.17]
Subtotal (95% CI)	135	141	-	41.59%	1.01[0.61,1.67]
Total events: 47 (Treatment), 48 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.49, df=1	.(P=0.48); I ² =0%				
Test for overall effect: Z=0.04(P=0.97)					
Total (95% CI)	402	403		100%	0.97[0.7,1.34]
Total events: 126 (Treatment), 124 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =3.17, df=7	r(P=0.87); I ² =0%				
Test for overall effect: Z=0.18(P=0.86)					
Test for subgroup differences: Chi ² =0.0	04, df=1 (P=0.84), I ² =	0%			
			0.1 0.2 0.5 1 2 5 10)	

Analysis 6.13. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
6.13.1 NaF					
Christiansen 1980	3/27	3/28		14.94%	1.04[0.19,5.59]
Grove 1981	2/14	4/14	↓	13.42%	0.44[0.07,2.6]
Subtotal (95% CI)	41	42		28.36%	0.69[0.2,2.35]
Total events: 5 (Treatment), 7 (Control)				
Heterogeneity: Tau ² =0; Chi ² =0.47, df=1	.(P=0.49); I ² =0%				
Test for overall effect: Z=0.59(P=0.56)					
6.13.2 MFP					
Gambacciani 1995	9/30	9/30	e	35.17%	1[0.33,2.99]
Sebert 1995	9/35	8/41		36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	65	71		71.64%	1.2[0.56,2.58]
Total events: 18 (Treatment), 17 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.2, df=1(P=0.65); I ² =0%				
Test for overall effect: Z=0.46(P=0.65)					
			0.1 0.2 0.5 1 2 5 1	10	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
Total (95% CI)	106	113				\blacklozenge				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, df	f=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.94	4)										
Test for subgroup differences: Chi ² =	0.55, df=1 (P=0.46), l ² =0%										
			0.1	0.2	0.5	1	2	5	10		

Analysis 6.14. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
6.14.1 NaF					
Hansson 1987	1/25	3/25	◀	3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	13.58%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101	_	36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	226	220	-	61.22%	0.98[0.63,1.54]
Total events: 74 (Treatment), 69 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =1.88, df=3	8(P=0.6); l ² =0%				
Test for overall effect: Z=0.07(P=0.94)					
6.14.2 MFP					
Reginster 1998	38/100	40/100	_ _	38.78%	0.92[0.52,1.62]
Subtotal (95% CI)	100	100		38.78%	0.92[0.52,1.62]
Total events: 38 (Treatment), 40 (Cont	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77)					
Total (95% CI)	326	320	•	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	I(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Chi ² =0.0	03, df=1 (P=0.86), I ² =0	9%			
			0.1 0.2 0.5 1 2 5 1	0	

Comparison 7. Sensitivity Dosage: Fluoride vs Placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 Low dose	3	540	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.74, 1.68]
1.2 High dose	1	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.39, 1.21]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 No. People with new vertebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 Low dose	3	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.24 [0.12, 0.49]
2.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.61, 1.55]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.65]
3.1 Low dose	6	800	Mean Difference (IV, Fixed, 95% CI)	8.12 [7.14, 9.09]
3.2 High dose	1	202	Mean Difference (IV, Fixed, 95% CI)	21.79 [19.12, 24.46]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 Low dose	2	299	Mean Difference (IV, Fixed, 95% CI)	10.84 [9.24, 12.43]
4.2 High dose	1	202	Mean Difference (IV, Fixed, 95% CI)	39.73 [35.77, 43.69]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 Low dose	7	859	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.96, 1.90]
5.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.37, 4.92]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 Low dose	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.2 High dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 Low dose	3	323	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.41 [2.30, 12.75]
7.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.37, 4.92]
8 Non vertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 Low dose	3	664	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.68, 1.77]
8.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.56 [2.19, 5.79]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.1 Low dose	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.2 High dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
10 Non vertebral frac- tures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 Low dose	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.45, 1.97]
10.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.56 [2.19, 5.79]
11 Lower limb pain syn- drome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
11.1 Low dose	4	721	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.35 [2.09, 5.39]
11.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.17 [2.44, 7.10]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.63, 1.17]
12.1 Low dose	7	579	Peto Odds Ratio (Peto, Fixed, 95% Cl)	0.95 [0.64, 1.42]
12.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.43, 1.19]
13 Withdrawals and dropouts 2 yeras	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 Low dose	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.2 High dose	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 Low dose	3	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.55, 1.50]
14.2 High dose	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.61, 1.66]

Analysis 7.1. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio				Weight	Peto Odds Ratio		
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
7.1.1 Low dose											
Meunier 1998	69/208	37/146				+-	<u> </u>			51.48%	1.45[0.91,2.3]
Pak 1995	6/54	16/56	_			-				12.66%	0.34[0.13,0.86]
Sebert 1995	2/35	1/41							→	2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	297	243				\blacklozenge				66.21%	1.12[0.74,1.68]
Total events: 77 (Treatment), 54 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =7.94, df	=2(P=0.02); I ² =74.81%										
Test for overall effect: Z=0.53(P=0.6)											
7.1.2 High dose							1				
			0.1	0.2	0.5	1	2	5	10		

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Study or subgroup	Treatment	Control	Peto Odo	ls Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	d, 95% CI		Peto, Fixed, 95% CI
Riggs 1990	33/101	42/101		_	33.79%	0.68[0.39,1.21]
Subtotal (95% CI)	101	101		•	33.79%	0.68[0.39,1.21]
Total events: 33 (Treatment), 42 (Cor	ntrol)					
Heterogeneity: Not applicable						
Test for overall effect: Z=1.31(P=0.19))					
Total (95% CI)	398	344	-		100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Co	ontrol)					
Heterogeneity: Tau ² =0; Chi ² =9.82, df	=3(P=0.02); I ² =69.44%					
Test for overall effect: Z=0.33(P=0.74))					
Test for subgroup differences: Chi ² =1	1.88, df=1 (P=0.17), I ² =46.	7%				
		0	1 02 05 1	2 5	10	

Analysis 7.2. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.2.1 Low dose					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	◀──────────────────────────────	7.77%	0.21[0.05,0.87]
Subtotal (95% CI)	179	181		30.46%	0.24[0.12,0.49]
Total events: 8 (Treatment), 30 (Contre	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.15, df=2	2(P=0.93); I ² =0%				
Test for overall effect: Z=3.9(P<0.0001)	1				
7.2.2 High dose					
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Riggs 1990	40/101	45/101	B	49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	147	139	-	69.54%	0.97[0.61,1.55]
Total events: 71 (Treatment), 67 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =1.29, df=1	L(P=0.26); I ² =22.23%				
Test for overall effect: Z=0.13(P=0.9)					
Total (95% CI)	326	320		100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df=	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Chi ² =10	.15, df=1 (P=0), I ² =90.	15%			
			0.1 0.2 0.5 1 2 5	10	

Analysis 7.3. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tre	atment	Control			Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed, 95% CI		Fixed, 95% CI
7.3.1 Low dose								
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		+	8.04%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)			1.18%	12.2[3.78,20.62]
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)			-+ 3%	8.4[3.11,13.69]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)		-	6.95%	9.34[5.86,12.82]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)			66.82%	8.04[6.92,9.16]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)			2.2%	11.06[4.88,17.24]
Subtotal ***	365		435				88.19 %	8.12[7.14,9.09]
Heterogeneity: Tau ² =0; Chi ² =3.63, df=	5(P=0.6)	; I ² =0%						
Test for overall effect: Z=16.3(P<0.000	1)							
7.3.2 High dose								
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)			11.81%	21.79[19.12,24.46]
Subtotal ***	101		101				11.81%	21.79[19.12,24.46]
Heterogeneity: Not applicable								
Test for overall effect: Z=16.02(P<0.00	01)							
Total ***	466		536				100%	9.73[8.82,10.65]
Heterogeneity: Tau ² =0; Chi ² =92.68, df	=6(P<0.0	0001); I ² =93.53%						
Test for overall effect: Z=20.82(P<0.00	01)							
Test for subgroup differences: Chi ² =89	9.05, df=	1 (P<0.0001), I ² =	98.88%					
					-10	-5 0 5	10	

Analysis 7.4. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	eatment	Control			Mean D	oifference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed	, 95% CI			Fixed, 95% CI
7.4.1 Low dose										
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)					4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					81.5%	10.4[8.76,12.04]
Subtotal ***	148		151					•	86.04%	10.84[9.24,12.43]
Heterogeneity: Tau ² =0; Chi ² =5.16, df=	1(P=0.02	2); I ² =80.62%								
Test for overall effect: Z=13.31(P<0.00	01)									
7.4.2 High dose										
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)					13.96%	39.73[35.77,43.69]
Subtotal ***	101		101						13.96%	39.73[35.77,43.69]
Heterogeneity: Not applicable										
Test for overall effect: Z=19.65(P<0.00	01)									
Total ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	lf=2(P<0	.0001); I ² =98.89%	1							
Test for overall effect: Z=19.69(P<0.00	01)									
Test for subgroup differences: Chi ² =17	75.75, df	=1 (P<0.0001), I ² =	99.43%							
					-10	-5	0 5	10		

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
7.5.1 Low dose					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	← →	1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25		2.22%	8.42[1.11,63.64]
Meunier 1998	123/208	87/146	_ 	49.11%	0.98[0.64,1.51]
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	437	422	◆	77.8%	1.35[0.96,1.9]
Total events: 160 (Treatment), 107 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =19.49, df	=6(P=0); I ² =69.22%				
Test for overall effect: Z=1.72(P=0.09)					
7.5.2 High dose					
Kleerekoper 1991	16/46	6/38	•	9.63%	2.64[1,6.97]
Riggs 1990	17/101	7/101	↓	12.57%	2.56[1.09,6]
Subtotal (95% CI)	147	139		22.2%	2.6[1.37,4.92]
Total events: 33 (Treatment), 13 (Cont	trol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.96); l ² =0%				
Test for overall effect: Z=2.92(P=0)					
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df	=8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ² =3.	13, df=1 (P=0.08), l ² =6	58.01%			
			0.1 0.2 0.5 1 2 5 10		

Analysis 7.5. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 5 GI minor overall.

Analysis 7.6. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.6.1 Low dose						
Gambacciani 1995	7/30	6/30			9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	◀		1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146			75.07%	0.98[0.64,1.51]
Sebert 1995	10/45	9/49		+	13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	297	239		•	100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 (C	Control)					
Heterogeneity: Tau ² =0; Chi ² =0.28, df	=3(P=0.96); I ² =0%					
Test for overall effect: Z=0.19(P=0.85))					
7.6.2 High dose						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Contr	ol)					
Heterogeneity: Not applicable						
			0.1 0.2	0.5 1 2	5 10	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Test for overall effect: Not applicab	le										
Total (95% CI)	297	239				\blacklozenge				100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28, c	df=3(P=0.96); I ² =0%										
Test for overall effect: Z=0.19(P=0.8	35)										
Test for subgroup differences: Not a	applicable				1						
			0.1	0.2	0.5	1	2	5	10		

Analysis 7.7. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.7.1 Low dose					
Hansson 1987	4/25	0/25	│───	6.42%	8.42[1.11,63.64]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Subtotal (95% CI)	140	183		35.81%	5.41[2.3,12.75]
Total events: 19 (Treatment), 4 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =7.2, df=2	(P=0.03); I ² =72.23%				
Test for overall effect: Z=3.86(P=0)					
7.7.2 High dose					
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Riggs 1990	17/101	7/101		36.35%	2.56[1.09,6]
Subtotal (95% CI)	147	139		64.19%	2.6[1.37,4.92]
Total events: 33 (Treatment), 13 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(F	P=0.96); I ² =0%				
Test for overall effect: Z=2.92(P=0)					
Total (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=	4(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.000	01)				
Test for subgroup differences: Chi ² =1.	.81, df=1 (P=0.18), I ² =4	14.87%			
		0.1	0.2 0.5 1 2 5 10	L	

Analysis 7.8. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control	Pet	o Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N	Peto	Fixed, 95% CI			Peto, Fixed, 95% CI
7.8.1 Low dose							
Meunier 1998	29/208	17/146				29.56%	1.22[0.65,2.3]
Pak 1995	3/54	5/56				5.69%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100	_	+		15.54%	1.1[0.46,2.62]
Subtotal (95% CI)	362	302		-		50.79%	1.1[0.68,1.77]
Total events: 44 (Treatment), 33 (Cont	rol)						
			0.1 0.2 0.5	1 2	5 10		

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	_				_							
Study or subgroup	Treatment	Control			Peto (Odds Ra	atio			Weight	Peto Odds R	atio
	n/N	n/N			Peto, Fi	ixed, 95	5% CI				Peto, Fixed, 9	5% CI
Heterogeneity: Tau ² =0; Chi ² =0.77, df	f=2(P=0.68); I ² =0%											
Test for overall effect: Z=0.38(P=0.71	.)											
7.8.2 High dose												
Kleerekoper 1991	13/46	7/38			-	-	+			11.61%	1.71[0	63,4.66]
Riggs 1990	61/101	24/101						-		37.6%	4.46[2	56,7.79]
Subtotal (95% CI)	147	139								49.21%	3.56[2.:	19,5.79]
Total events: 74 (Treatment), 31 (Co	ntrol)											
Heterogeneity: Tau ² =0; Chi ² =2.69, df	f=1(P=0.1); l ² =62.8%											
Test for overall effect: Z=5.11(P<0.00	001)											
Total (95% CI)	509	441				-				100%	1.96[1.3	39,2.75]
Total events: 118 (Treatment), 64 (Ce	ontrol)											
Heterogeneity: Tau ² =0; Chi ² =14.84, c	df=4(P=0.01); l ² =73.05%											
Test for overall effect: Z=3.85(P=0)												
Test for subgroup differences: Chi ² =:	11.39, df=1 (P=0), I ² =91.22	%										
			0.1	0.2	0.5	1	2	5 1	10			

Analysis 7.9. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.9.1 Low dose					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
7.9.2 High dose					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not appli	cable				
		0.1	0.2 0.5 1 2 5	10	

Analysis 7.10. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment n/N	Control n/N			Peto Peto, F	Odds ixed,	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
7.10.1 Low dose											
			0.1	0.2	0.5	1	2	5	10		

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Study or subgroup	Treatment	Control	Peto O	dds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fix	ced, 95% CI		Peto, Fixed, 95% CI
Pak 1995	3/54	5/56	+		8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100			22.07%	1.1[0.46,2.62]
Subtotal (95% CI)	154	156			30.14%	0.94[0.45,1.97]
Total events: 15 (Treatment), 16 (Co	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =0.48, df	f=1(P=0.49); I ² =0%					
Test for overall effect: Z=0.16(P=0.87	7)					
7.10.2 High dose						
Kleerekoper 1991	13/46	7/38		+-+	16.49%	1.71[0.63,4.66]
Riggs 1990	61/101	24/101		— —	53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	147	139			69.86%	3.56[2.19,5.79]
Total events: 74 (Treatment), 31 (Co	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =2.69, df	f=1(P=0.1); I ² =62.8%					
Test for overall effect: Z=5.11(P<0.00	001)					
Total (95% CI)	301	295		-	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Co	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =11.81, o	df=3(P=0.01); I ² =74.59%					
Test for overall effect: Z=4.18(P<0.00	001)					
Test for subgroup differences: Chi ² =	8.64, df=1 (P=0), l ² =88.429	6				
			0.1 0.2 0.5	1 2 5 10)	

Analysis 7.11. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.11.1 Low dose					
Meunier 1998	37/208	7/146	_	30.59%	3.29[1.73,6.24]
Pak 1995	6/54	8/56		10.07%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Sebert 1995	5/45	2/49		5.34%	2.74[0.59,12.71]
Subtotal (95% CI)	368	353		55.85%	3.35[2.09,5.39]
Total events: 62 (Treatment), 17 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =15.61, df=	=3(P=0); I ² =80.78%				
Test for overall effect: Z=5(P<0.0001)					
7.11.2 High dose					
Kleerekoper 1991	23/46	13/38	+	16.85%	1.89[0.8,4.48]
Riggs 1990	37/101	5/101		27.3%	6.78[3.44,13.36]
Subtotal (95% CI)	147	139		44.15%	4.17[2.44,7.1]
Total events: 60 (Treatment), 18 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =5.2, df=1(P=0.02); I ² =80.78%				
Test for overall effect: Z=5.25(P<0.0001	L)				
Total (95% CI)	515	492	•	100%	3.69[2.59,5.26]
Total events: 122 (Treatment), 35 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =21.16, df=	=5(P=0); I ² =76.38%				
Test for overall effect: Z=7.22(P<0.0001	L)				
Test for subgroup differences: Chi ² =0.3	36, df=1 (P=0.55), l ² =0	0%			
		0.1	0.2 0.5 1 2 5 10		

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Analysis 7.12. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 12 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
7.12.1 Low dose					
Christiansen 1980	3/27	3/28		3.49%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30		8.22%	1[0.33,2.99]
Grove 1981	2/14	4/14	↓	3.14%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	↓	2.41%	0.34[0.05,2.61]
Pak 1995	6/54	5/56		6.41%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100	_ _	30.68%	0.92[0.52,1.62]
Sebert 1995	9/35	8/41	+	8.53%	1.42[0.49,4.17]
Subtotal (95% CI)	285	294	-	62.87%	0.95[0.64,1.42]
Total events: 68 (Treatment), 72 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =2.47, df=6	6(P=0.87); I ² =0%				
Test for overall effect: Z=0.24(P=0.81)					
7.12.2 High dose					
Kleerekoper 1991	32/46	29/38		10.75%	0.72[0.27,1.86]
Riggs 1990	25/101	32/101		26.38%	0.71[0.39,1.31]
Subtotal (95% CI)	147	139		37.13%	0.71[0.43,1.19]
Total events: 57 (Treatment), 61 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=	=0.99); l ² =0%				
Test for overall effect: Z=1.29(P=0.2)					
Total (95% CI)	432	433	•	100%	0.86[0.63,1.17]
Total events: 125 (Treatment), 133 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =3.24, df=8	8(P=0.92); I ² =0%				
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi ² =0.7	7, df=1 (P=0.38), I ² =	0%			
			0.1 0.2 0.5 1 2 5 1	0	

Analysis 7.13. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 13 Withdrawals and dropouts 2 yeras.

Study or subgroup	Treatment	Control		Peto Odds Ratio			Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fix	ed, 95% CI			Peto, Fixed, 95% Cl
7.13.1 Low dose								
Christiansen 1980	3/27	3/28			+		14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30			-		35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	←	+	<u> </u>		13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41			-	-	36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	106	113					100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ontrol)							
Heterogeneity: Tau ² =0; Chi ² =1.23, d	f=3(P=0.75); I ² =0%							
Test for overall effect: Z=0.07(P=0.94	4)							
7.13.2 High dose								
Subtotal (95% CI)	0	0						Not estimable
			0.1 0	.2 0.5	1 2	5 10		

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Study or subgroup	Treatment	Control			Peto	Odds R	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% Cl
Total events: 0 (Treatment), 0 (Con	trol)										
Heterogeneity: Not applicable											
Test for overall effect: Not applicab	le										
Total (95% CI)	106	113				\blacklozenge	-			100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, c	lf=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.9	4)										
Test for subgroup differences: Not a	applicable				1						
			0.1 (0.2	0.5	1	2	5	10		

Analysis 7.14. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
7.14.1 Low dose					
Hansson 1987	1/25	3/25	↓	3.05%	0.34[0.05,2.61]
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100		38.78%	0.92[0.52,1.62]
Subtotal (95% CI)	179	181	-	49.92%	0.91[0.55,1.5]
Total events: 45 (Treatment), 48 (0	Control)				
Heterogeneity: Tau ² =0; Chi ² =1.17,	df=2(P=0.56); I ² =0%				
Test for overall effect: Z=0.36(P=0.	.72)				
7.14.2 High dose					
Kleerekoper 1991	32/46	29/38	+	13.58%	0.72[0.27,1.86]
Riggs 1990	35/101	32/101		36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	147	139	-	50.08%	1.01[0.61,1.66]
Total events: 67 (Treatment), 61 (Control)				
Heterogeneity: Tau ² =0; Chi ² =0.67,	df=1(P=0.41); I ² =0%				
Test for overall effect: Z=0.02(P=0.	.98)				
Total (95% CI)	326	320	•	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109	9 (Control)				
Heterogeneity: Tau ² =0; Chi ² =1.91,	df=4(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.	.81)				
Test for subgroup differences: Chi	² =0.07, df=1 (P=0.79), I ² =	0%			
			0.1 0.2 0.5 1 2 5 1	.0	

Comparison 8. Sensitivity Quality

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 Low quality	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.2 High quality	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 No. Peiple with new vertebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 Low quality	3	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.36, 0.90]
2.2 High quality	2	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.41, 1.82]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.65]
3.1 Low quality	6	802	Mean Difference (IV, Fixed, 95% CI)	13.14 [11.55, 14.73]
3.2 High quality	1	200	Mean Difference (IV, Fixed, 95% CI)	8.04 [6.92, 9.16]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 Low quality	2	301	Mean Difference (IV, Fixed, 95% CI)	34.57 [31.13, 38.01]
4.2 High quality	1	200	Mean Difference (IV, Fixed, 95% CI)	10.40 [8.76, 12.04]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 Low quality	8	1061	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [1.07, 2.03]
5.2 High quality	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.64 [1.00, 6.97]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 Low quality	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.2 High quality	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 Low quality	4	525	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.71 [2.03, 6.79]
7.2 High quality	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.64 [1.00, 6.97]
8 Non vertebral fractures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 Low quality	3	666	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [1.51, 3.37]
8.2 High quality	2	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.69, 2.56]
9 Non vertebral fractures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
9.1 Low quality	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.2 High quality	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Non vertebral frac- tures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 Low quality	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [2.04, 5.77]
10.2 High quality	2	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.69, 2.56]
11 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
11.1 Low quality	6	526	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.70, 1.60]
11.2 High quality	3	339	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.55, 1.40]
12 Lower limb pain syn- drome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
12.1 Low quality	5	923	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.23 [2.87, 6.23]
12.2 High quality	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.80, 4.48]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 Low quality	3	164	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.51, 2.07]
13.2 High quality	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.19, 5.59]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 Low quality	3	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.65, 1.80]
14.2 High quality	2	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.53, 1.40]

Analysis 8.1. Comparison 8 Sensitivity Quality, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio		Weight	Peto Odds Ratio	
	n/N	n/N	Peto, Fiz	xed, 95% CI			Peto, Fixed, 95% Cl
8.1.1 Low quality							
Meunier 1998	69/208	37/146		+		51.48%	1.45[0.91,2.3]
Pak 1995	6/54	16/56	+			12.66%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		+		33.79%	0.68[0.39,1.21]
Sebert 1995	2/35	1/41		+ +	\rightarrow	2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	398	344	•	•		100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Co	ntrol)						
	Fa	vours Treatment	0.1 0.2 0.5	1 2	5 10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	Fixed, 9	95% CI			-	Peto, Fixed, 95% Cl
Heterogeneity: Tau ² =0; Chi ² =9.82, df=3	8(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74)											
8.1.2 High quality											
Subtotal (95% CI)	0	0									Not estimable
Total events: 0 (Treatment), 0 (Control)										
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Total (95% CI)	398	344				\blacklozenge				100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Con	itrol)										
Heterogeneity: Tau ² =0; Chi ² =9.82, df=3	8(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74)											
Test for subgroup differences: Not app	licable										
	Favo	urs Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 8.2. Comparison 8 Sensitivity Quality, Outcome 2 No. Peiple with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
8.2.1 Low quality					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Riggs 1990	40/101	45/101	— — —	49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	180	182		72.49%	0.57[0.36,0.9]
Total events: 47 (Treatment), 68 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =5.41, df=2	2(P=0.07); I ² =63.02%				
Test for overall effect: Z=2.41(P=0.02)					
8.2.2 High quality					
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Reginster 1998	1/100	7/100	← ← ←	7.77%	0.21[0.05,0.87]
Subtotal (95% CI)	146	138		27.51%	0.86[0.41,1.82]
Total events: 32 (Treatment), 29 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =5.31, df=1	(P=0.02); I ² =81.16%				
Test for overall effect: Z=0.39(P=0.7)					
Total (95% CI)	326	320	•	100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df=	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Chi ² =0.8	87, df=1 (P=0.35), I ² =0%	þ			
	Favo	urs Treatment	0.1 0.2 0.5 1 2 5 1	¹⁰ Favours Control	

Study or subgroup	Tre	eatment	c	Control	Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.3.1 Low quality							
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		• 8.04%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)		1.18%	12.2[3.78,20.62]
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)			8.4[3.11,13.69]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)		6.95%	9.34[5.86,12.82]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)		11.81%	21.79[19.12,24.46]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)		2.2%	11.06[4.88,17.24]
Subtotal ***	366		436			33.18%	13.14[11.55,14.73]
Heterogeneity: Tau ² =0; Chi ² =66.28, c	lf=5(P<0.	0001); I ² =92.46%					
Test for overall effect: Z=16.19(P<0.0	001)						
8.3.2 High quality							
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)		66.82%	8.04[6.92,9.16]
Subtotal ***	100		100			66.82%	8.04[6.92,9.16]
Heterogeneity: Not applicable							
Test for overall effect: Z=14.06(P<0.0	001)						
Total ***	466		536			100%	9.73[8.82.10.65]
Heterogeneity: $Tau^2=0$: Chi ² =92.68 c	lf=6/P<0	0001)· I ² =93 53%				• -••	
Test for overall effect: 7=20 82/P<0.0	001)	5551/, F 55.5570					
Test for subgroup differences: Chi2=	001)	(D<0.0001) 12-0	C 2104				
rest for subgroup differences: ChI*=.	20.4, ui=1	L (P<0.0001), I*=9	0.21%			1	
			Favo	urs Treatment	-10 -5 0 5	10 Favours Cor	itrol

Analysis 8.3. Comparison 8 Sensitivity Quality, Outcome 3 Lumbar BMD % 2 years from baseline.

Analysis 8.4. Comparison 8 Sensitivity Quality, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	eatment	Control		Mean Di	fference	۱	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed,	95% CI			Fixed, 95% CI
8.4.1 Low quality									
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)				4.53%	18.68[11.73,25.63]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5))	13.96%	39.73[35.77,43.69]
Subtotal ***	149		152					18.5%	34.57[31.13,38.01]
Heterogeneity: Tau ² =0; Chi ² =26.58, df	=1(P<0.	0001); I ² =96.24%							
Test for overall effect: Z=19.68(P<0.00	01)								
8.4.2 High quality									
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)			-▶	81.5%	10.4[8.76,12.04]
Subtotal ***	100		100				◄	81.5%	10.4[8.76,12.04]
Heterogeneity: Not applicable									
Test for overall effect: Z=12.43(P<0.00	01)								
Total ***	249		252					100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, c	lf=2(P<0	.0001); I ² =98.89%							
Test for overall effect: Z=19.69(P<0.00	01)								
Test for subgroup differences: Chi ² =1	54.33, df	=1 (P<0.0001), I ² =	99.35%						
			Favou	irs Treatment	-10 -5	5	10 F	avours Contr	ol

Analysis 8.5. Comparison 8 Sensitivity Quality, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
8.5.1 Low quality					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	← →	1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25		2.22%	8.42[1.11,63.64]
Meunier 1998	123/208	87/146	_ _	49.11%	0.98[0.64,1.51]
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	│ ─── + ───	12.57%	2.56[1.09,6]
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	538	523	•	90.37%	1.48[1.07,2.03]
Total events: 177 (Treatment), 114 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =21.38, df=	7(P=0); I ² =67.25%				
Test for overall effect: Z=2.4(P=0.02)					
8.5.2 High quality					
Kleerekoper 1991	16/46	6/38	•	9.63%	2.64[1,6.97]
Subtotal (95% CI)	46	38		9.63%	2.64[1,6.97]
Total events: 16 (Treatment), 6 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.96(P=0.05)					
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df=	8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ² =1.2	25, df=1 (P=0.26), I ² =:	19.75%			
	Fa	vours Treatment (0.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 8.6. Comparison 8 Sensitivity Quality, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio	W	eight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI			Peto, Fixed, 95% CI
8.6.1 Low quality							
Gambacciani 1995	7/30	6/30		+	_	9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	◀			1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146		_ _		75.07%	0.98[0.64,1.51]
Sebert 1995	10/45	9/49		+		13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	297	239		+		100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 (Con	ntrol)						
Heterogeneity: Tau ² =0; Chi ² =0.28, df=3	(P=0.96); I ² =0%						
Test for overall effect: Z=0.19(P=0.85)							
8.6.2 High quality							
Subtotal (95% CI)	0	0					Not estimable
Total events: 0 (Treatment), 0 (Control))						
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
	Fa	vours Treatment	0.1 0.2	0.5 1 2	5 ¹⁰ Favour	s Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	297	239				\blacklozenge	•			100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28,	df=3(P=0.96); l ² =0%										
Test for overall effect: Z=0.19(P=0.3	85)										
Test for subgroup differences: Not	applicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 8.7. Comparison 8 Sensitivity Quality, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
8.7.1 Low quality					
Hansson 1987	4/25	0/25	· · · · · · · · · · · · · · · · · · ·	6.42%	8.42[1.11,63.64]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	-	36.35%	2.56[1.09,6]
Subtotal (95% CI)	241	284		72.15%	3.71[2.03,6.79]
Total events: 36 (Treatment), 11 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =8.68, df=3	B(P=0.03); I ² =65.42%				
Test for overall effect: Z=4.26(P<0.000)	1)				
8.7.2 High quality					
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Subtotal (95% CI)	46	38		27.85%	2.64[1,6.97]
Total events: 16 (Treatment), 6 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.96(P=0.05)					
Total (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	4(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001	1)				
Test for subgroup differences: Chi ² =0.3	34, df=1 (P=0.56), I ² =0	%			
	Fav	ours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 8.8. Comparison 8 Sensitivity Quality, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
8.8.1 Low quality											
Meunier 1998	29/208	17/146			_	-+•				29.56%	1.22[0.65,2.3]
Pak 1995	3/54	5/56	-		+	_				5.69%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101						-	-	37.6%	4.46[2.56,7.79]
Subtotal (95% CI)	363	303					\blacklozenge			72.84%	2.26[1.51,3.37]
Total events: 93 (Treatment), 46 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =12.59,	df=2(P=0); I ² =84.11%										
Test for overall effect: Z=3.99(P<0.00	001)										
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Patio	Weight	Peto Odds Patio
Study of Subgroup	n/N	n/N	Peto Guus Ratio	weight	Peto Ouds Ratio
	11/ N	11/19	reto, rixed, 55% Ci		Felo, Fixed, 55% Ci
8.8.2 High quality					
Kleerekoper 1991	13/46	7/38	+	- 11.61%	1.71[0.63,4.66]
Reginster 1998	12/100	11/100		15.54%	1.1[0.46,2.62]
Subtotal (95% CI)	146	138		27.16%	1.33[0.69,2.56]
Total events: 25 (Treatment), 18 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =0.42, d	lf=1(P=0.52); I ² =0%				
Test for overall effect: Z=0.85(P=0.3	9)				
Total (95% CI)	509	441	•	100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (0	Control)				
Heterogeneity: Tau ² =0; Chi ² =14.84,	df=4(P=0.01); I ² =73.05%	6			
Test for overall effect: Z=3.85(P=0)					
Test for subgroup differences: Chi ² =	=1.83, df=1 (P=0.18), I ² =4	45.37%			
	Fa	vours Treatment 0	0.1 0.2 0.5 1 2	5 10 Fayours Control	

Analysis 8.9. Comparison 8 Sensitivity Quality, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Freatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
8.9.1 Low quality					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
8.9.2 High quality					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Control	.)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not applic	able				

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 8.10. Comparison 8 Sensitivity Quality, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio			Weight	Peto Odds Ratio				
	n/N	n/N			Peto, F	ixed	, 95% CI				Peto, Fixed, 95% CI
8.10.1 Low quality											
Pak 1995	3/54	5/56	-		•					8.07%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101					-	-	_ ,	53.37%	4.46[2.56,7.79]
	F	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Subtotal (95% CI)	155	157		61.45%	3.43[2.04,5.77]
Total events: 64 (Treatment), 29 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =6.44, d	f=1(P=0.01); I ² =84.48%				
Test for overall effect: Z=4.66(P<0.00	001)				
8.10.2 High quality					
Kleerekoper 1991	13/46	7/38		16.49%	1.71[0.63,4.66]
Reginster 1998	12/100	11/100		22.07%	1.1[0.46,2.62]
Subtotal (95% CI)	146	138		38.55%	1.33[0.69,2.56]
Total events: 25 (Treatment), 18 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.42, d	f=1(P=0.52); I ² =0%				
Test for overall effect: Z=0.85(P=0.39))				
Total (95% CI)	301	295	-	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =11.81, o	df=3(P=0.01); I ² =74.59%)			
Test for overall effect: Z=4.18(P<0.00	001)				
Test for subgroup differences: Chi ² =	4.94, df=1 (P=0.03), I ² =7	9.77%			
	Fav	ours Treatment 0.1	L 0.2 0.5 1 2 5 1	¹⁰ Favours Control	

Analysis 8.11. Comparison 8 Sensitivity Quality, Outcome 11 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
8.11.1 Low quality					
Gambacciani 1995	9/30	9/30	_	8.02%	1[0.33,2.99]
Grove 1981	2/14	4/14	↓ ↓	3.06%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	┥	2.35%	0.34[0.05,2.61]
Pak 1995	6/54	5/56		6.25%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101	_	28.17%	1.14[0.64,2.05]
Sebert 1995	9/35	8/41		8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	259	267	-	56.17%	1.06[0.7,1.6]
Total events: 62 (Treatment), 61 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =2.57, df=5	5(P=0.77); I ² =0%				
Test for overall effect: Z=0.27(P=0.79)					
8.11.2 High quality					
Christiansen 1980	3/27	3/28		3.41%	1.04[0.19,5.59]
Kleerekoper 1991	32/46	29/38	+	10.49%	0.72[0.27,1.86]
Reginster 1998	38/100	40/100	_ _	29.93%	0.92[0.52,1.62]
Subtotal (95% CI)	173	166		43.83%	0.87[0.55,1.4]
Total events: 73 (Treatment), 72 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.24, df=2	2(P=0.89); I ² =0%				
Test for overall effect: Z=0.56(P=0.57)					
Total (95% CI)	432	433	•	100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =3.17, df=8	3(P=0.92); I ² =0%				
Test for overall effect: Z=0.17(P=0.86)					
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% Cl						Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	
Test for subgroup differences: Chi ² =0.36, df=1 (P=0.55), I ² =0%				I			1				
	F	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 8.12. Comparison 8 Sensitivity Quality, Outcome 12 Lower limb pain syndrome.

n/N n/N Peto, Fixed, 95% CI Peto, Fixed, 95% CI 8.12.1 Low quality Meunier 1998 37/208 7/146 30.59% 3.29[1.73, 6.24 Pak 1995 6/54 8/56 10.07% 0.75[0.25, 2.3] Riggs 1982 14/61 0/102 → 9.85% 18.27[5.91, 56.42] Riggs 1990 37/101 5/101 → 27.3% 6.78[3.44, 13.36] Sebert 1995 5/45 2/49 → 5.34% 2.74[0.59, 12.71] Subtotal (95% CI) 469 454 ▲ 83.15% 4.23[2.87, 6.23] Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% ★ 83.15% 4.23[2.87, 6.23] 8.12.2 High quality Kleerekoper 1991 23/46 13/38 ▲ 456 ★ 858 Subtotal (95% CI) 46 38 ▲ 16.85% 1.89[0.8, 4.48] Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable 16.85% 1.89[0.8, 4.48]	Study or subgroup
8.12.1 Low quality Meunier 1998 37/208 7/146 Pak 1995 6/54 8/56 Riggs 1982 14/61 0/102 Riggs 1990 37/101 5/101 Sebert 1995 5/45 2/49 Subtotal (95% CI) 469 454 Total events: 99 (Treatment), 22 (Control) 469 454 Heterogeneity: Tau²=0; Chi²=18.39, df=4(P=0); l²=78.25% 83.15% 4.23[2.87,6.23 Test for overall effect: Z=7.27(P<0.0001) 466 38 Subtotal (95% CI) 46 38 Total events: 23 (Treatment), 13 (Control) 466 38 Heterogeneity: Not applicable 16.85% 1.89[0.8,4.48]	
Meunier 1998 37/208 7/146 30.59% 3.29[1.73,6.24 Pak 1995 6/54 8/56 10.07% 0.75[0.25,2.2] Riggs 1982 14/61 0/102 9.85% 18.27[5.91,56.44 Riggs 1990 37/101 5/101 27.3% 6.78[3.44,13.36 Sebert 1995 5/45 2/49 5.34% 2.74[0.59,12.71 Subtotal (95% Cl) 469 454 83.15% 4.23[2.87,6.23 Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% 83.15% 1.89[0.8,4.48 Subtotal (95% Cl) 46 38 16.85% 1.89[0.8,4.48 Total events: 23 (Treatment), 13 (Control) 46 38 16.85% 1.89[0.8,4.48 Heterogeneity: Not applicable 13/38 16.85% 1.89[0.8,4.48 1.89[0.8,4.48	8.12.1 Low quality
Pak 1995 6/54 8/56 10.07% 0.75[0.25,2.: Riggs 1982 14/61 0/102 9.85% 18.27[5.91,56.44] Riggs 1990 37/101 5/101 27.3% 6.78[3.44,13.36] Sebert 1995 5/45 2/49 5.34% 2.74[0.59,12.7] Subtotal (95% Cl) 469 454 83.15% 4.23[2.87,6.23] Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² -0; Chi ² =18.39, df=4(P=0); I ² =78.25% 8.12.2 High quality 16.85% 1.89[0.8,4.48] Kleerekoper 1991 23/46 13/38 16.85% 1.89[0.8,4.48] Total events: 23 (Treatment), 13 (Control) 46 38 16.85% 1.89[0.8,4.48] Heterogeneity: Not applicable 46 38 6 1.89[0.8,4.48] 1.89[0.8,4.48]	Meunier 1998
Riggs 1982 14/61 0/102 9.85% 18.27[5.91,56.44 Riggs 1990 37/101 5/101 27.3% 6.78[3.44,13.34 Sebert 1995 5/45 2/49 5.34% 2.74[0.59,12.71 Subtotal (95% CI) 469 454 83.15% 4.23[2.87,6.23 Total events: 99 (Treatment), 22 (Control) 469 454 83.15% 4.23[2.87,6.23 Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% Test for overall effect: Z=7.27(P<0.0001)	Pak 1995
Riggs 1990 37/101 5/101 27.3% 6.78[3.44,13.36] Sebert 1995 5/45 2/49 5.34% 2.74[0.59,12.7] Subtotal (95% CI) 469 454 83.15% 4.23[2.87,6.23] Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% 8.12.2 High quality 16.85% 1.89[0.8,4.48] Kleerekoper 1991 23/46 13/38 16.85% 1.89[0.8,4.48] Subtotal (95% CI) 46 38 16.85% 1.89[0.8,4.48] Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable 189[0.8,4.48] 16.85% 1.89[0.8,4.48]	Riggs 1982
Sebert 1995 5/45 2/49 5.34% 2.74[0.59,12.7: Subtotal (95% CI) 469 454 83.15% 4.23[2.87,6.2: Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% 83.15% 4.23[2.87,6.2: Test for overall effect: Z=7.27(P<0.0001)	Riggs 1990
Subtotal (95% Cl)46945483.15%4.23[2.87,6.25%Total events: 99 (Treatment), 22 (Control)Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25%Image: Chi ² =18.39, df=4(P=0); l ² =78.25%Image: Chi ² =18.39, df=4(P=0); l ² =78.25%Test for overall effect: Z=7.27(P<0.0001)	Sebert 1995
Total events: 99 (Treatment), 22 (Control) Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); l ² =78.25% Test for overall effect: Z=7.27(P<0.0001)	Subtotal (95% CI)
Heterogeneity: Tau ² =0; Chi ² =18.39, df=4(P=0); I ² =78.25% Test for overall effect: Z=7.27(P<0.0001) 8.12.2 High quality Kleerekoper 1991 23/46 13/38 Subtotal (95% Cl) 46 38 Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable	Total events: 99 (Treatment), 22 (Con
Test for overall effect: Z=7.27(P<0.0001)	Heterogeneity: Tau ² =0; Chi ² =18.39, df
8.12.2 High quality Kleerekoper 1991 23/46 13/38 16.85% 1.89[0.8,4.48 Subtotal (95% Cl) 46 38 16.85% 1.89[0.8,4.48 Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable 16.85% 1.89[0.8,4.48	Test for overall effect: Z=7.27(P<0.000
8.12.2 High quality Kleerekoper 1991 23/46 13/38 16.85% 1.89[0.8,4.48 Subtotal (95% Cl) 46 38 16.85% 1.89[0.8,4.48 Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable 16.85% 1.89[0.8,4.48	
Kleerekoper 1991 23/46 13/38 + 16.85% 1.89[0.8,4.48 Subtotal (95% Cl) 46 38 - 16.85% 1.89[0.8,4.48 Total events: 23 (Treatment), 13 (Control) -	8.12.2 High quality
Subtotal (95% CI)463816.85%1.89[0.8,4.48Total events: 23 (Treatment), 13 (Control)Heterogeneity: Not applicable	Kleerekoper 1991
Total events: 23 (Treatment), 13 (Control) Heterogeneity: Not applicable	Subtotal (95% CI)
Heterogeneity: Not applicable	Total events: 23 (Treatment), 13 (Con
	Heterogeneity: Not applicable
Test for overall effect: Z=1.45(P=0.15)	Test for overall effect: Z=1.45(P=0.15)
Total (95% CI) 515 492 🔶 100% 3.69[2.59,5.26	Total (95% CI)
Total events: 122 (Treatment), 35 (Control)	Total events: 122 (Treatment), 35 (Co
Heterogeneity: Tau ² =0; Chi ² =21.16, df=5(P=0); l ² =76.38%	Heterogeneity: Tau ² =0; Chi ² =21.16, df
Test for overall effect: Z=7.22(P<0.0001)	Test for overall effect: Z=7.22(P<0.000
Test for subgroup differences: Chi ² =2.77, df=1 (P=0.1), I ² =63.94%	Test for subgroup differences: Chi ² =2.
Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control	

Analysis 8.13. Comparison 8 Sensitivity Quality, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control			Peto O	dds Ra	tio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fix	ed, 95	% CI				Peto, Fixed, 95% CI
8.13.1 Low quality											
Gambacciani 1995	9/30	9/30				+				35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	←		+	-				13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41				+ -		-		36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	79	85				\rightarrow	-			85.06%	1.02[0.51,2.07]
Total events: 20 (Treatment), 21 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, d	f=2(P=0.54); I ² =0%										
Test for overall effect: Z=0.06(P=0.9	5)										
8.13.2 High quality											
Christiansen 1980	3/27	3/28				+				14.94%	1.04[0.19,5.59]
	F	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment n/N	Control n/N			Peto Peto, F	Odds Fixed, 1	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
Subtotal (95% CI)	27	28								14.94%	1.04[0.19,5.59]
Total events: 3 (Treatment), 3 (Control	l)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.05(P=0.96)											
Total (95% CI)	106	113				\blacklozenge				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Cont	rol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, df=3	3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.94)											
Test for subgroup differences: Chi ² =0,	df=1 (P=0.98), I ² =0%										
	Favo	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 8.14. Comparison 8 Sensitivity Quality, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
8.14.1 Low quality					
Hansson 1987	1/25	3/25	↓	3.05%	0.34[0.05,2.61]
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101		36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	180	182	-	47.64%	1.08[0.65,1.8]
Total events: 42 (Treatment), 40 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =1.33, df=2	2(P=0.52); I ² =0%				
Test for overall effect: Z=0.29(P=0.77)					
8.14.2 High quality					
Kleerekoper 1991	32/46	29/38	+	13.58%	0.72[0.27,1.86]
Reginster 1998	38/100	40/100	_ _	38.78%	0.92[0.52,1.62]
Subtotal (95% CI)	146	138	-	52.36%	0.86[0.53,1.4]
Total events: 70 (Treatment), 69 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.2, df=1(P=0.66); I ² =0%				
Test for overall effect: Z=0.6(P=0.55)					
Total (95% CI)	326	320	•	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	I(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Chi ² =0.3	39, df=1 (P=0.53), l ² =0	0%			
	-		01 02 05 1 2 5 1		

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Comparison 9. Subgroup men/women

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size		
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]		

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 With men	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [0.23, 23.42]
1.2 Without men	3	666	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.66, 1.30]
2 No. People with new vertebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.46, 1.01]
2.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Without men	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.46, 1.01]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.65]
3.1 With men	1	59	Mean Difference (IV, Fixed, 95% CI)	11.06 [4.88, 17.24]
3.2 Without men	6	943	Mean Difference (IV, Fixed, 95% CI)	9.70 [8.78, 10.63]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 With men	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Without men	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 With men	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.46, 3.45]
5.2 Without men	8	1051	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [1.16, 2.19]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 With men	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.46, 3.45]
6.2 Without men	3	442	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.67, 1.50]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Without men	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
8 Non vertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Without men	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
9.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Without men	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
10 Non vertebral frac- tures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Without men	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
11 Lower limb pain syn- drome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
11.1 With men	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [0.59, 12.71]
11.2 Without men	5	913	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.75 [2.61, 5.40]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
12.1 With men	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.49, 4.17]
12.2 Without men	8	789	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.68, 1.30]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 With men	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.49, 4.17]
13.2 Without men	3	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.38, 1.92]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 With men	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Without men	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]

Analysis 9.1. Comparison 9 Subgroup men/women, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control			Peto 0	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	ixed, 9	95% CI				Peto, Fixed, 95% Cl
9.1.1 With men											
Sebert 1995	2/35	1/41				_			→	2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	35	41		_						2.07%	2.35[0.23,23.42]
Total events: 2 (Treatment), 1 (Control)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.73(P=0.47)											
	Fa	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto,	Fixed, 9	95% CI			-	Peto, Fixed, 95% CI
9.1.2 Without men											
Meunier 1998	69/208	37/146				+-				51.48%	1.45[0.91,2.3]
Pak 1995	6/54	16/56	-		•	_				12.66%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101								33.79%	0.68[0.39,1.21]
Subtotal (95% CI)	363	303				\blacklozenge				97.93%	0.93[0.66,1.3]
Total events: 108 (Treatment), 95 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =9.21, df=	=2(P=0.01); I ² =78.28%										
Test for overall effect: Z=0.44(P=0.66)	1										
Total (95% CI)	398	344				\bullet				100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =9.82, df=	=3(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74)	1										
Test for subgroup differences: Chi ² =0	.61, df=1 (P=0.43), l ² =00	%									
	Favo	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 9.2. Comparison 9 Subgroup men/women, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
9.2.1 With men					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.2.2 Without men					
Hansson 1987	0/25	1/25	↓	1.02%	0.14[0,6.82]
Kleerekoper 1991	35/46	22/38	+	18.73%	2.28[0.91,5.69]
Pak 1995	7/54	22/56		21.96%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	↓	7.87%	0.21[0.05,0.87]
Riggs 1990	40/101	45/101		50.43%	0.82[0.47,1.43]
Subtotal (95% CI)	326	320		100%	0.68[0.46,1.01]
Total events: 83 (Treatment), 97 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =15.37, df=	4(P=0); I ² =73.98%				
Test for overall effect: Z=1.91(P=0.06)					
Total (95% CI)	326	320	•	100%	0.68[0.46,1.01]
Total events: 83 (Treatment), 97 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =15.37, df=	4(P=0); I ² =73.98%				
Test for overall effect: Z=1.91(P=0.06)					
Test for subgroup differences: Not appl	licable				
	Fav	ours Treatment	0.1 0.2 0.5 1 2 5 1	¹⁰ Favours Control	
Analysis 9.3. Comparison 9 Subgroup men/women, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tre	eatment	Control		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
9.3.1 With men							
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)		2.2%	11.06[4.88,17.24]
Subtotal ***	26		33			2.2%	11.06[4.88,17.24]
Heterogeneity: Tau ² =0; Chi ² =0, df=0(F	<0.0001	.); I ² =100%					
Test for overall effect: Z=3.51(P=0)							
9.3.2 Without men							
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		8.04%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)		1.18%	12.2[3.78,20.62]
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)	· · · · · · · · · · · · · · · · · · ·	3%	8.4[3.11,13.69]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)		6.95%	9.34[5.86,12.82]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)		66.82%	8.04[6.92,9.16]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)	▶	11.81%	21.79[19.12,24.46]
Subtotal ***	440		503		•	97.8%	9.7[8.78,10.63]
Heterogeneity: Tau ² =0; Chi ² =92.5, df=	5(P<0.0	001); l ² =94.59%					
Test for overall effect: Z=20.52(P<0.00	01)						
Total ***	466		536		•	100%	9.73[8.82,10.65]
Heterogeneity: Tau ² =0; Chi ² =92.68, df	=6(P<0.	0001); I ² =93.53%					
Test for overall effect: Z=20.82(P<0.00	01)						
Test for subgroup differences: Chi ² =0.	18, df=1	. (P=0.67), I ² =0%					
			Favoi	urs Treatment	-10 -5 0 5 10	Favours Con	trol

Analysis 9.4. Comparison 9 Subgroup men/women, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	atment	Control			Mean	Difference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixe	d, 95% CI			Fixed, 95% CI
9.4.1 With men										
Subtotal ***	0		0							Not estimable
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
9.4.2 Without men										
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)				►	4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					81.5%	10.4[8.76,12.04]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)				►	13.96%	39.73[35.77,43.69]
Subtotal ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	f=2(P<0	.0001); I ² =98.89%								
Test for overall effect: Z=19.69(P<0.000	01)									
Total ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	f=2(P<0	.0001); I ² =98.89%								
Test for overall effect: Z=19.69(P<0.000	D1)									
Test for subgroup differences: Not app	licable									
			Favou	rs Treatment	-10	-5	0 5	5 10	Favours Co	ontrol

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Analysis 9.5. Comparison 9 Subgroup men/women, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
9.5.1 With men					
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	45	49		9.05%	1.27[0.46,3.45]
Total events: 10 (Treatment), 9 (Co	ntrol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.6	54)				
9.5.2 Without men					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14		1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25		2.22%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38	• • • • • •	9.63%	2.64[1,6.97]
Meunier 1998	123/208	87/146		49.11%	0.98[0.64,1.51]
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	+	12.57%	2.56[1.09,6]
Subtotal (95% CI)	539	512	◆	90.95%	1.59[1.16,2.19]
Total events: 183 (Treatment), 111	(Control)				
Heterogeneity: Tau ² =0; Chi ² =22.44,	df=7(P=0); I ² =68.8%				
Test for overall effect: Z=2.89(P=0)					
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120	(Control)				
Heterogeneity: Tau ² =0; Chi ² =22.62,	df=8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ²	=0.18, df=1 (P=0.67), l ² =	0%			
	Fa	vours Treatment 0.1	0.2 0.5 1 2 5 1	0 Favours Control	

Analysis 9.6. Comparison 9 Subgroup men/women, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control			Peto	Odds R	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% Cl
9.6.1 With men											
Sebert 1995	10/45	9/49				+				13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	45	49								13.83%	1.27[0.46,3.45]
Total events: 10 (Treatment), 9 (Contro	ol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.46(P=0.64)											
9.6.2 Without men											
Gambacciani 1995	7/30	6/30				+•		_		9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	-			-			\rightarrow	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146			-	-				75.07%	0.98[0.64,1.51]
Subtotal (95% CI)	252	190			-	\blacklozenge				86.17%	1[0.67,1.5]
Total events: 131 (Treatment), 94 (Con	trol)										
Heterogeneity: Tau ² =0; Chi ² =0.1, df=2(P=0.95); I ² =0%										
Test for overall effect: Z=0.02(P=0.98)											
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	297	239				\blacklozenge				100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28,	df=3(P=0.96); I ² =0%										
Test for overall effect: Z=0.19(P=0.	85)										
Test for subgroup differences: Chi ⁴	² =0.18, df=1 (P=0.67), I ² =0	%			1						
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 9.7. Comparison 9 Subgroup men/women, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
9.7.1 With men					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)	1				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.7.2 Without men					
Hansson 1987	4/25	0/25		6.42%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		36.35%	2.56[1.09,6]
Subtotal (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
Total (95% CI)	287	322	•	100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
Test for subgroup differences: Not appl	licable				
	Fav	ours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 9.8. Comparison 9 Subgroup men/women, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control			Peto O	dds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fix	ked,	95% CI				Peto, Fixed, 95% CI
9.8.1 With men											
Subtotal (95% CI)	0	0									Not estimable
Total events: 0 (Treatment), 0 (Control)	1										
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
9.8.2 Without men											
Kleerekoper 1991	13/46	7/38			. —	-	+	— .		11.61%	1.71[0.63,4.66]
	I	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	P	eto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Pet	o, Fixed, 95% CI		Peto, Fixed, 95% Cl
Meunier 1998	29/208	17/146			29.56%	1.22[0.65,2.3]
Pak 1995	3/54	5/56		+	5.69%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100	-		15.54%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101		_ _	- 37.6%	4.46[2.56,7.79]
Subtotal (95% CI)	509	441		-	100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (Cor	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =14.84, df	=4(P=0.01); I ² =73.05%					
Test for overall effect: Z=3.85(P=0)						
Total (95% CI)	509	441		•	100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (Cor	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =14.84, df	=4(P=0.01); I ² =73.05%					
Test for overall effect: Z=3.85(P=0)						
Test for subgroup differences: Not app	olicable					
	Fav	ours Treatment	0.1 0.2 0.	5 1 2 5	¹⁰ Favours Control	

Analysis 9.9. Comparison 9 Subgroup men/women, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
9.9.1 With men					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.9.2 Without men					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Total (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not applie	cable				
	F.		02 05 1 2 5	10 5	

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 9.10. Comparison 9 Subgroup men/women, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
9.10.1 With men											
Subtotal (95% CI)	0	0									Not estimable
Total events: 0 (Treatment), 0 (Control)										
	Fa	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.10.2 Without men					
Kleerekoper 1991	13/46	7/38		16.49%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	+	8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100		22.07%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101	——————————————————————————————————————	53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	301	295	•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.81, df=	3(P=0.01); I ² =74.59%				
Test for overall effect: Z=4.18(P<0.0001	.)				
Total (95% CI)	301	295	•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.81, df=	3(P=0.01); I ² =74.59%				
Test for overall effect: Z=4.18(P<0.0001	.)				
Test for subgroup differences: Not app	licable				
	Favo	ours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 9.11. Comparison 9 Subgroup men/women, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
9.11.1 With men					
Sebert 1995	5/45	2/49		5.34%	2.74[0.59,12.71]
Subtotal (95% CI)	45	49		5.34%	2.74[0.59,12.71]
Total events: 5 (Treatment), 2 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					
9.11.2 Without men					
Kleerekoper 1991	23/46	13/38	+	16.85%	1.89[0.8,4.48]
Meunier 1998	37/208	7/146		30.59%	3.29[1.73,6.24]
Pak 1995	6/54	8/56	+	10.07%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101		27.3%	6.78[3.44,13.36]
Subtotal (95% CI)	470	443	•	94.66%	3.75[2.61,5.4]
Total events: 117 (Treatment), 33 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =21.01, df=	4(P=0); I ² =80.96%				
Test for overall effect: Z=7.12(P<0.0001	L)				
Total (95% CI)	515	492	•	100%	3.69[2.59,5.26]
Total events: 122 (Treatment), 35 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =21.16, df=	5(P=0); I ² =76.38%				
Test for overall effect: Z=7.22(P<0.0001	L)				
Test for subgroup differences: Chi ² =0.1	15, df=1 (P=0.7), I ² =0	%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
9.12.1 With men					
Sebert 1995	9/35	8/41		8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	35	41		8.32%	1.42[0.49,4.17]
Total events: 9 (Treatment), 8 (Contr	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)				
9.12.2 Without men					
Christiansen 1980	3/27	3/28		3.41%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30	+	8.02%	1[0.33,2.99]
Grove 1981	2/14	4/14	+ +	3.06%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	+	2.35%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	10.49%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		6.25%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100	_	29.93%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101		28.17%	1.14[0.64,2.05]
Subtotal (95% CI)	397	392	•	91.68%	0.94[0.68,1.3]
Total events: 126 (Treatment), 125 (C	Control)				
Heterogeneity: Tau ² =0; Chi ² =2.65, df	=7(P=0.92); I ² =0%				
Test for overall effect: Z=0.37(P=0.71)				
Total (95% CI)	432	433	+	100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (C	Control)				
Heterogeneity: Tau ² =0; Chi ² =3.17, df	=8(P=0.92); I ² =0%				
Test for overall effect: Z=0.17(P=0.86)				
Test for subgroup differences: Chi ² =0	0.52, df=1 (P=0.47), I ² =	0%			
	Fa	wours Treatment	0.1 0.2 0.5 1 2 5	10 Eavours Control	

Analysis 9.12. Comparison 9 Subgroup men/women, Outcome 12 Withdrawals and dropouts overall.

Favours Treatment Favours Control

Analysis 9.13. Comparison 9 Subgroup men/women, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control		Peto Od	ds Ratio		Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI				Peto, Fixed, 95% CI
9.13.1 With men								
Sebert 1995	9/35	8/41				-	36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	35	41				-	36.48%	1.42[0.49,4.17]
Total events: 9 (Treatment), 8 (Control)	1							
Heterogeneity: Not applicable								
Test for overall effect: Z=0.64(P=0.52)								
9.13.2 Without men								
Christiansen 1980	3/27	3/28			•		14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30					35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	←	+			13.42%	0.44[0.07,2.6]
Subtotal (95% CI)	71	72					63.52%	0.85[0.38,1.92]
Total events: 14 (Treatment), 16 (Contr	ol)							
Heterogeneity: Tau ² =0; Chi ² =0.67, df=2	(P=0.72); I ² =0%							
Test for overall effect: Z=0.39(P=0.69)								
	Fa	vours Treatment	0.1	0.2 0.5	1 2	5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control		Peto		Peto Odds Ratio				Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	xed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	106	113				\bullet				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (0	Control)										
Heterogeneity: Tau ² =0; Chi ² =1.23,	df=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.	94)										
Test for subgroup differences: Chi	² =0.56, df=1 (P=0.45), I ² =0	%			1						
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 9.14. Comparison 9 Subgroup men/women, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
9.14.1 With men					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.14.2 Without men					
Hansson 1987	1/25	3/25	↓ ↓	3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	· · · · · · · · · · · · · · · · · · ·	13.58%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100		38.78%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101		36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	326	320	•	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Total (95% CI)	326	320		100%	0 96[0 67 1 36]
Total events: 112 (Treatment) 100 (Co	strol)	520		100/0	0.50[0.01,1.50]
Total events: 112 (Treatment), 109 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Not app	licable				
	Fa	avours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Comparison 10. Subgroup Vit D/ no vit D = EC/Non EC

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new ver- tebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.91, 2.30]
1.2 Without vit D = non EC	3	388	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.37, 0.97]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 No. People with new ver- tebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Without vit D = non EC	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.65]
3.1 With vit D = EC	1	354	Mean Difference (IV, Fixed, 95% CI)	8.40 [3.11, 13.69]
3.2 Without vit D = non EC	6	648	Mean Difference (IV, Fixed, 95% CI)	9.77 [8.84, 10.70]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 With vit D = EC	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Without vit D = non EC	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.64, 1.51]
5.2 Without vit D = non EC	8	791	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [1.60, 3.72]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.64, 1.51]
6.2 Without vit D = non EC	3	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.58, 2.59]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Without vit D = Non EC	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
8 Non vertebral fractures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
8.2 Without vit D = non EC	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
9 Non vertebral fractures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.2 Without vit D = non EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
10 Non vertebral fractures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Without vit D = non EC	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
11 Lower limb pain syn- drome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
11.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.29 [1.73, 6.24]
11.2 Without vit D = non EC	5	653	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.88 [2.54, 5.94]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
12.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Without vit D = non EC	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Without vit D = non EC	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Without vit D = non EC	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]

Analysis 10.1. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control	Peto Odo	ls Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	d, 95% CI		Peto, Fixed, 95% CI
10.1.1 With vit D = EC						
Meunier 1998	69/208	37/146	+		51.48%	1.45[0.91,2.3]
Subtotal (95% CI)	208	146	•		51.48%	1.45[0.91,2.3]
Total events: 69 (Treatment), 37 (Cont	rol)					
Heterogeneity: Not applicable						
Test for overall effect: Z=1.58(P=0.11)						
10.1.2 Without vit D = non EC						
Pak 1995	6/54	16/56			12.66%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		-	33.79%	0.68[0.39,1.21]
	Fa	vours Treatment	0.1 0.2 0.5 1	2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control		Peto Odds Ratio			Weight	Peto Odds Ratio			
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Sebert 1995	2/35	1/41								2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	190	198								48.52%	0.6[0.37,0.97]
Total events: 41 (Treatment), 59 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =3, df=2(P=0.22); I ² =33.25%										
Test for overall effect: Z=2.1(P=0.04)											
Total (95% CI)	398	344			•	\blacklozenge				100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =9.82, df	=3(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74)										
Test for subgroup differences: Chi ² =6	5.82, df=1 (P=0.01), I ² =8	35.34%									
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 10.2. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
10.2.1 With vit D = EC					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.2.2 Without vit D = non EC					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	↓ → → → → → → → → → → → → → → → → → → →	7.77%	0.21[0.05,0.87]
Riggs 1990	40/101	45/101	— — —	49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	326	320		100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Total (95% CI)	326	320		100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Not app	olicable				
	Favo	urs Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 10.3. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tr	eatment	c	Control	Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
10.3.1 With vit D = EC							
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)	+	3%	8.4[3.11,13.69]
Subtotal ***	146		208			3%	8.4[3.11,13.69]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.11(P=0)							
10.2.2 Without with D - non EC							
	21	105 (2.4)	21	00.0 (C.0)		0.040/	C 2[2 07 0 42]
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		8.04%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)		1.18%	12.2[3.78,20.62]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)		6.95%	9.34[5.86,12.82]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)		66.82%	8.04[6.92,9.16]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)		11.81%	21.79[19.12,24.46]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)		2.2%	11.06[4.88,17.24]
Subtotal ***	320		328		•	97%	9.77[8.84,10.7]
Heterogeneity: Tau ² =0; Chi ² =92.43, o	df=5(P<0.	0001); l ² =94.59%					
Test for overall effect: Z=20.59(P<0.0	0001)						
Total ***	166		E26			100%	0 72[9 92 10 65]
	400		530		•	100%	9.73[8.82,10.85]
Heterogeneity: Tau ² =0; Chi ² =92.68, o	df=6(P<0.	0001); l ² =93.53%					
Test for overall effect: Z=20.82(P<0.0	0001)						
Test for subgroup differences: Chi ² =	0.25, df=:	L (P=0.62), I ² =0%					
			Favo	urs Treatment	-10 -5 0 5 10	Favours Co	ntrol

Analysis 10.4. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	atment	c	ontrol		Mean Difference			Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed,	95% CI			Fixed, 95% CI
10.4.1 With vit D = EC										
Subtotal ***	0		0							Not estimable
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
10.4.2 Without vit D = non EC										
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)					4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					81.5%	10.4[8.76,12.04]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)					13.96%	39.73[35.77,43.69]
Subtotal ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	lf=2(P<0	.0001); I ² =98.89%)							
Test for overall effect: Z=19.69(P<0.00	01)									
Total ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	lf=2(P<0	.0001); I ² =98.89%)							
Test for overall effect: Z=19.69(P<0.00	01)									
Test for subgroup differences: Not app	olicable									
			Favou	urs Treatment	-10 -	5	0 5	5 10	Favours Co	ontrol

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
10.5.1 With vit D = EC					
Meunier 1998	123/208	87/146	— <u>+</u> —	49.11%	0.98[0.64,1.51]
Subtotal (95% CI)	208	146	-	49.11%	0.98[0.64,1.51]
Total events: 123 (Treatment), 87 (Co	ntrol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					
10.5.2 Without vit D = non EC					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	$\longleftarrow \qquad \rightarrow$	1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25	│ →	2.22%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		9.63%	2.64[1,6.97]
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	+	12.57%	2.56[1.09,6]
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	376	415	-	50.89%	2.44[1.6,3.72]
Total events: 70 (Treatment), 33 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =13.85, df	=7(P=0.05); I ² =49.47%	ó			
Test for overall effect: Z=4.14(P<0.000	1)				
Total (95% CI)	584	561	◆	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df	=8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ² =8.	.77, df=1 (P=0), l ² =88.0	5%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 10	⁾ Favours Control	

Analysis 10.5. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 5 GI minor overall.

Analysis 10.6. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
10.6.1 With vit D = EC											
Meunier 1998	123/208	87/146			-	-	-			75.07%	0.98[0.64,1.51]
Subtotal (95% CI)	208	146			-	\blacklozenge				75.07%	0.98[0.64,1.51]
Total events: 123 (Treatment), 87 (Con	itrol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.09(P=0.93)											
10.6.2 Without vit D = non EC											
Gambacciani 1995	7/30	6/30				+		_		9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	←						\rightarrow	1.74%	1[0.06,16.85]
Sebert 1995	10/45	9/49				+				13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	89	93			-					24.93%	1.23[0.58,2.59]
Total events: 18 (Treatment), 16 (Cont	rol)										
Heterogeneity: Tau ² =0; Chi ² =0.02, df=2	2(P=0.99); I ² =0%			1	i						
	Fa	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
Test for overall effect: Z=0.53(P=0.5	59)										
Total (95% CI)	297	239				\blacklozenge				100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28,	df=3(P=0.96); I ² =0%										
Test for overall effect: Z=0.19(P=0.8	85)										
Test for subgroup differences: Chi ²	² =0.26, df=1 (P=0.61), I ² =0	1%							1		
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 10.7. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
10.7.1 With vit D = EC					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.7.2 Without vit D = Non EC					
Hansson 1987	4/25	0/25	· · · · · · · · · · · · · · · · · · ·	6.42%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		36.35%	2.56[1.09,6]
Subtotal (95% CI)	287	322	-	100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
Total (95% CI)	287	322		100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.0001)				
Test for subgroup differences: Not app	licable				
	Fav	/ours Treatment 0	.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 10.8. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control		Peto Odds Ratio				Weight	Peto Odds Ratio		
	n/N	n/N			Peto, Fi	ixed,	95% CI				Peto, Fixed, 95% CI
10.8.1 With vit D = EC											
Meunier 1998	29/208	17/146			_	-+•	—			29.56%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146			-					29.56%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	ol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.63(P=0.53)											
	F	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI			-	Peto, Fixed, 95% Cl
10.8.2 Without vit D = non EC											
Kleerekoper 1991	13/46	7/38			-		+			11.61%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	-		+					5.69%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100				+				15.54%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101					_	-	_	37.6%	4.46[2.56,7.79]
Subtotal (95% CI)	301	295					•	•		70.44%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (C	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =11.81,	df=3(P=0.01); I ² =74.59%										
Test for overall effect: Z=4.18(P<0.0	0001)										
Total (95% CI)	509	441					\blacklozenge			100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (Control)										
Heterogeneity: Tau ² =0; Chi ² =14.84,	df=4(P=0.01); I ² =73.05%										
Test for overall effect: Z=3.85(P=0)											
Test for subgroup differences: Chi ²	=3.03, df=1 (P=0.08), I ² =6	7.04%									
	Fay	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 10.9. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
10.9.1 With vit D = EC					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
10.9.2 Without vit D = non EC					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not applie	cable				
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 10.10. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment n/N	Control n/N		Peto Odds Ratio Peto, Fixed, 95% Cl						Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
10.10.1 With vit D = EC							1				
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Od	ds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	d, 95% CI		Peto, Fixed, 95% CI
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.10.2 Without vit D = non EC						
Kleerekoper 1991	13/46	7/38		+	16.49%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	+		8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100		+	22.07%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101			- 53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	301	295		•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Con	trol)					
Heterogeneity: Tau ² =0; Chi ² =11.81, df	=3(P=0.01); I ² =74.59%					
Test for overall effect: Z=4.18(P<0.000	1)					
Total (95% CI)	301	295		•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Con	trol)					
Heterogeneity: Tau ² =0; Chi ² =11.81, df	=3(P=0.01); I ² =74.59%					
Test for overall effect: Z=4.18(P<0.000	1)					
Test for subgroup differences: Not app	olicable					
	Favo	ours Treatment	0.1 0.2 0.5 1	. 2 5	¹⁰ Favours Control	

Analysis 10.11. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
10.11.1 With vit D = EC					
Meunier 1998	37/208	7/146		30.59%	3.29[1.73,6.24]
Subtotal (95% CI)	208	146		30.59%	3.29[1.73,6.24]
Total events: 37 (Treatment), 7 (Cont	trol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=3.64(P=0)					
10.11.2 Without vit D = non EC					
Kleerekoper 1991	23/46	13/38	+	16.85%	1.89[0.8,4.48]
Pak 1995	6/54	8/56	+	10.07%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101		27.3%	6.78[3.44,13.36]
Sebert 1995	5/45	2/49		5.34%	2.74[0.59,12.71]
Subtotal (95% CI)	307	346	•	69.41%	3.88[2.54,5.94]
Total events: 85 (Treatment), 28 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =20.99, d	lf=4(P=0); I ² =80.94%				
Test for overall effect: Z=6.25(P<0.00	01)				
Total (95% CI)	515	492	•	100%	3.69[2.59,5.26]
Total events: 122 (Treatment), 35 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =21.16, d	lf=5(P=0); I ² =76.38%				
Test for overall effect: Z=7.22(P<0.00	01)				
Test for subgroup differences: Chi ² =0	0.18, df=1 (P=0.67), I ² =0	0%			
	Fav	vours Treatment ^{0.}	1 0.2 0.5 1 2 5 10	Favours Control	

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Analysis 10.12. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 12 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
10.12.1 With vit D = EC					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.12.2 Without vit D = non EC					
Christiansen 1980	3/27	3/28		3.41%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30	_	8.02%	1[0.33,2.99]
Grove 1981	2/14	4/14	· · · · · · · · · · · · · · · · · · ·	3.06%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	↓	2.35%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	10.49%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		6.25%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100		29.93%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101		28.17%	1.14[0.64,2.05]
Sebert 1995	9/35	8/41		8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	432	433	•	100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =3.17, df=8	(P=0.92); I ² =0%				
Test for overall effect: Z=0.17(P=0.86)					
Total (95% CI)	432	433	•	100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (Con	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =3.17, df=8	(P=0.92); I ² =0%				
Test for overall effect: Z=0.17(P=0.86)					
Test for subgroup differences: Not app	licable				
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 10.13 Comparison 10 Subgroup Vit D/ no vit D = FC/

Analysis 10.13. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control	Peto Od	ds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% Cl
10.13.1 With vit D = EC						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control))					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.13.2 Without vit D = non EC						
Christiansen 1980	3/27	3/28		•	14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30		•	35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14			13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41		-	36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	106	113			100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Contr	ol)					
	Fa	vours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Heterogeneity: Tau ² =0; Chi ² =1.	23, df=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P	2=0.94)										
Total (95% CI)	106	113				\bullet				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 2	4 (Control)										
Heterogeneity: Tau ² =0; Chi ² =1.	23, df=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P	9=0.94)										
Test for subgroup differences:	Not applicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 10.14. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI			Peto, Fixed, 95% CI
10.14.1 With vit D = EC							
Subtotal (95% CI)	0	0					Not estimable
Total events: 0 (Treatment), 0 (Con	itrol)						
Heterogeneity: Not applicable							
Test for overall effect: Not applicat	ble						
10.14.2 Without vit D = non EC							
Hansson 1987	1/25	3/25	◀──	+		3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	-			13.58%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		•		8.1%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100				38.78%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101				36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	326	320		+		100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109	(Control)						
Heterogeneity: Tau ² =0; Chi ² =1.91,	df=4(P=0.75); I ² =0%						
Test for overall effect: Z=0.23(P=0.8	31)						
Total (95% CI)	326	320		+		100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109	(Control)						
Heterogeneity: Tau ² =0; Chi ² =1.91,	df=4(P=0.75); I ² =0%						
Test for overall effect: Z=0.23(P=0.8	31)						
Test for subgroup differences: Not	applicable						
	Fa	vours Treatment	0.1 0.2	0.5 1 2	5 10	Favours Control	

Comparison 11. Subgroup HRT/non HRT

Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 HRT	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.13, 0.86]
1.2 Non HRT	3	632	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.77, 1.56]
2 No. People with new vertebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 HRT	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.12, 0.51]
2.2 Non HRT	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.59, 1.51]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.64]
3.1 HRT	2	299	Mean Difference (IV, Fixed, 95% CI)	8.17 [7.11, 9.23]
3.2 Non HRT	5	703	Mean Difference (IV, Fixed, 95% CI)	14.15 [12.36, 15.94]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 HRT	2	299	Mean Difference (IV, Fixed, 95% CI)	10.84 [9.24, 12.43]
4.2 Non HRT	1	202	Mean Difference (IV, Fixed, 95% CI)	39.73 [35.77, 43.69]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 HRT	2	273	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.91 [1.91, 12.65]
5.2 Non HRT	7	872	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [1.00, 1.88]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 HRT	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Non HRT	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
7 GI minor 4 years	5	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.02, 5.64]
7.1 HRT	2	273	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.91 [1.91, 12.65]
7.2 Non HRT	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.89 [1.57, 5.32]
8 Non vertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 HRT	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.45, 1.97]
8.2 Non HRT	3	640	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.62, 3.50]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
9.1 HRT	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Non HRT	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
10 Non vertebral frac- tures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 HRT	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.45, 1.97]
10.2 Non HRT	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.56 [2.19, 5.79]
11 Lower limb pain syndrome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
11.1 HRT	2	273	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.65 [1.65, 8.06]
11.2 Non HRT	4	734	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.70 [2.49, 5.50]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
12.1 HRT	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.58, 1.63]
12.2 Non HRT	7	555	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.66, 1.44]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 HRT	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Non HRT	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 HRT	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.58, 1.63]
14.2 Non HRT	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.58, 1.54]

Analysis 11.1. Comparison 11 Subgroup HRT/non HRT, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control		Peto Odds Ratio					Weight	Peto Odds Ratio	
	n/N	n/N			Peto, Fi	ixed, S	95% CI				Peto, Fixed, 95% Cl
11.1.1 HRT											
Pak 1995	6/54	16/56	-		•	-				12.66%	0.34[0.13,0.86]
Subtotal (95% CI)	54	56	-			-				12.66%	0.34[0.13,0.86]
Total events: 6 (Treatment), 16 (Contr	ol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=2.28(P=0.02)											
	Fav	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, I	Fixed, 9	95% CI			-	Peto, Fixed, 95% Cl
11.1.2 Non HRT											
Meunier 1998	69/208	37/146				+•				51.48%	1.45[0.91,2.3]
Riggs 1990	33/101	42/101				-				33.79%	0.68[0.39,1.21]
Sebert 1995	2/35	1/41							→	2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	344	288				+	•			87.34%	1.1[0.77,1.56]
Total events: 104 (Treatment), 80 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =4.47, df	=2(P=0.11); I ² =55.3%										
Test for overall effect: Z=0.51(P=0.61))										
Total (95% CI)	398	344				•				100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =9.82, df	=3(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74))										
Test for subgroup differences: Chi ² =5	.34, df=1 (P=0.02), I ² =8	31.28%									
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 11.2. Comparison 11 Subgroup HRT/non HRT, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.2.1 HRT					
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	← →	7.77%	0.21[0.05,0.87]
Subtotal (95% CI)	154	156		29.45%	0.25[0.12,0.51]
Total events: 8 (Treatment), 29 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.06, df=1	L(P=0.8); I ² =0%				
Test for overall effect: Z=3.78(P=0)					
11.2.2 Non HRT					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Riggs 1990	40/101	45/101		49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	172	164		70.55%	0.94[0.59,1.51]
Total events: 71 (Treatment), 68 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =2.24, df=2	2(P=0.33); I ² =10.79%				
Test for overall effect: Z=0.24(P=0.81)					
Total (95% CI)	326	320	•	100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df=	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Chi ² =9.2	28, df=1 (P=0), I ² =89.2	2%			
	Fav	ours Treatment	0.1 0.2 0.5 1 2 5 1	¹⁰ Favours Control	

Analysis 11.3. Comparison 11 Subgroup HRT/non HRT, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tre	atment	Control		Mean Di	fference	Weight M	lean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed,	95% CI		Fixed, 95% CI
11.3.1 HRT								
Pak 1995	48	109.6 (10.3)	51	100.3 (6)			7.48%	9.34[6,12.68]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)			66.44%	8.04[6.92,9.16]
Subtotal ***	148		151			•	73.92%	8.17[7.11,9.23]
Heterogeneity: Tau ² =0; Chi ² =0.52, df=	1(P=0.47	7); I ² =0%						
Test for overall effect: Z=15.07(P<0.00	01)							
11.3.2 Non HRT								
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)			7.99%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)			1.18%	12.2[3.78,20.62]
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)			2.98%	8.4[3.11,13.69]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)			11.74%	21.79[19.12,24.46]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)			2.19%	11.06[4.88,17.24]
Subtotal ***	318		385				26.08%	14.15[12.36,15.94]
Heterogeneity: Tau ² =0; Chi ² =60.47, df	=4(P<0.0	0001); I ² =93.39%						
Test for overall effect: Z=15.5(P<0.000	1)							
Total ***	466		536			•	100%	9.73[8.82,10.64]
Heterogeneity: Tau ² =0; Chi ² =92.68, df	=6(P<0.0	0001); I ² =93.53%						
Test for overall effect: Z=20.87(P<0.00	01)							
Test for subgroup differences: Chi ² =31	69, df=	1 (P<0.0001), I ² =9	6.84%					
			Favou	urs Treatment	-10 -5 0	0 5 10	Favours Control	

Analysis 11.4. Comparison 11 Subgroup HRT/non HRT, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	atment	Control		Mean Difference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% Cl			Fixed, 95% CI
11.4.1 HRT								
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)			4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)			81.5%	10.4[8.76,12.04]
Subtotal ***	148		151			•	86.04%	10.84[9.24,12.43]
Heterogeneity: Tau ² =0; Chi ² =5.16, df=	1(P=0.02	2); I ² =80.62%						
Test for overall effect: Z=13.31(P<0.00	01)							
11.4.2 Non HRT								
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)			13.96%	39.73[35.77,43.69]
Subtotal ***	101		101				13.96%	39.73[35.77,43.69]
Heterogeneity: Not applicable								
Test for overall effect: Z=19.65(P<0.00	01)							
Total ***	249		252				100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	f=2(P<0	.0001); I ² =98.89%						
Test for overall effect: Z=19.69(P<0.00	01)							
Test for subgroup differences: Chi ² =17	5.75, df	=1 (P<0.0001), I ² =	99.43%					
			Favou	rs Treatment	-10 -5 0 5	10	Favours Cor	ntrol

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Analysis 11.5. Comparison 11 Subgroup HRT/non HRT, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.5.1 HRT					
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Subtotal (95% CI)	115	158		10.16%	4.91[1.91,12.65]
Total events: 15 (Treatment), 4 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =6.98, df=1	(P=0.01); I ² =85.67%				
Test for overall effect: Z=3.3(P=0)					
11.5.2 Non HRT					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	← →	1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25	│ ▶	2.22%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38	•	9.63%	2.64[1,6.97]
Meunier 1998	123/208	87/146	— — —	49.11%	0.98[0.64,1.51]
Riggs 1990	17/101	7/101		12.57%	2.56[1.09,6]
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	469	403	◆	89.84%	1.37[1,1.88]
Total events: 178 (Treatment), 116 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =9.35, df=6	(P=0.15); I ² =35.83%				
Test for overall effect: Z=1.94(P=0.05)					
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df=	8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ² =6.2	29, df=1 (P=0.01), l ² =8	34.11%			
	Fav	vours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 11.6. Comparison 11 Subgroup HRT/non HRT, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.6.1 HRT					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control	l)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.6.2 Non HRT					
Gambacciani 1995	7/30	6/30		9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	← →	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146		75.07%	0.98[0.64,1.51]
Sebert 1995	10/45	9/49		13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	297	239	•	100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.28, df=3	8(P=0.96); I ² =0%				
Test for overall effect: Z=0.19(P=0.85)					
		Favours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	297	239				\blacklozenge	•			100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28,	df=3(P=0.96); l ² =0%										
Test for overall effect: Z=0.19(P=0.3	85)										
Test for subgroup differences: Not	applicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 11.7. Comparison 11 Subgroup HRT/non HRT, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.7.1 HRT					
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		15.13%	16.93[4.53,63.26]
Subtotal (95% CI)	115	158		29.39%	4.91[1.91,12.65]
Total events: 15 (Treatment), 4 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =6.98, df=1	(P=0.01); I ² =85.67%				
Test for overall effect: Z=3.3(P=0)					
11.7.2 Non HRT					
Hansson 1987	4/25	0/25	→ I	6.42%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Riggs 1990	17/101	7/101		36.35%	2.56[1.09,6]
Subtotal (95% CI)	172	164		70.61%	2.89[1.57,5.32]
Total events: 37 (Treatment), 13 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =1.18, df=2	2(P=0.55); I ² =0%				
Test for overall effect: Z=3.41(P=0)					
Total (95% CI)	287	322	-	100%	3.38[2.02,5.64]
Total events: 52 (Treatment), 17 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =9.02, df=4	(P=0.06); I ² =55.64%				
Test for overall effect: Z=4.65(P<0.000)	L)				
Test for subgroup differences: Chi ² =0.8	86, df=1 (P=0.35), I ² =0	0%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 11.8. Comparison 11 Subgroup HRT/non HRT, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control			Peto (Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	ixed, S	95% CI				Peto, Fixed, 95% Cl
11.8.1 HRT											
Pak 1995	3/54	5/56	-		+					5.69%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100				+				15.54%	1.1[0.46,2.62]
Subtotal (95% CI)	154	156								21.23%	0.94[0.45,1.97]
Total events: 15 (Treatment), 16 (Con	itrol)										
Heterogeneity: Tau ² =0; Chi ² =0.48, df=	=1(P=0.49); I ² =0%										
Test for overall effect: Z=0.16(P=0.87)											
					1						
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
11.8.2 Non HRT											
Kleerekoper 1991	13/46	7/38			_	_	+			11.61%	1.71[0.63,4.66]
Meunier 1998	29/208	17/146			-					29.56%	1.22[0.65,2.3]
Riggs 1990	61/101	24/101						-	_	37.6%	4.46[2.56,7.79]
Subtotal (95% CI)	355	285					\blacklozenge	•		78.77%	2.38[1.62,3.5]
Total events: 103 (Treatment), 48 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =9.6, df=2	(P=0.01); I ² =79.16%										
Test for overall effect: Z=4.42(P<0.000	1)										
Total (95% CI)	509	441					•			100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =14.84, df	=4(P=0.01); I ² =73.05%										
Test for overall effect: Z=3.85(P=0)											
Test for subgroup differences: Chi ² =4.	76, df=1 (P=0.03), I ² =7	8.99%		1							
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 11.9. Comparison 11 Subgroup HRT/non HRT, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
11.9.1 HRT					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.9.2 Non HRT					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Total (95% CI)	208	146		100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not appli	icable				
		01	0.2 0.5 1 2 5	10 5 6 1 1	

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 11.10. Comparison 11 Subgroup HRT/non HRT, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
11.10.1 HRT											
Pak 1995	3/54	5/56			•	-				8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100				•				22.07%	1.1[0.46,2.62]
	Fa	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Subtotal (95% CI)	154	156		30.14%	0.94[0.45,1.97]
Total events: 15 (Treatment), 16 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =0.48, o	df=1(P=0.49); I ² =0%				
Test for overall effect: Z=0.16(P=0.8	37)				
11.10.2 Non HRT					
Kleerekoper 1991	13/46	7/38		16.49%	1.71[0.63,4.66]
Riggs 1990	61/101	24/101		53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	147	139		69.86%	3.56[2.19,5.79]
Total events: 74 (Treatment), 31 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =2.69, o	df=1(P=0.1); I ² =62.8%				
Test for overall effect: Z=5.11(P<0.0	0001)				
Total (95% CI)	301	295	\bullet	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =11.81,	df=3(P=0.01); l ² =74.59%				
Test for overall effect: Z=4.18(P<0.0	0001)				
Test for subgroup differences: Chi ²	=8.64, df=1 (P=0), I ² =88.4	2%			
	Fav	ours Treatment 0.1	0.2 0.5 1 2 5 10	⁾ Favours Control	

Analysis 11.11. Comparison 11 Subgroup HRT/non HRT, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.11.1 HRT					
Pak 1995	6/54	8/56	+	10.07%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Subtotal (95% CI)	115	158		19.92%	3.65[1.65,8.06]
Total events: 20 (Treatment), 8 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =15.49, df	=1(P<0.0001); I ² =93.5	55%			
Test for overall effect: Z=3.19(P=0)					
11.11.2 Non HRT					
Kleerekoper 1991	23/46	13/38	+ +	16.85%	1.89[0.8,4.48]
Meunier 1998	37/208	7/146	-	30.59%	3.29[1.73,6.24]
Riggs 1990	37/101	5/101		27.3%	6.78[3.44,13.36]
Sebert 1995	5/45	2/49		5.34%	2.74[0.59,12.71]
Subtotal (95% CI)	400	334	•	80.08%	3.7[2.49,5.5]
Total events: 102 (Treatment), 27 (Con	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =5.67, df=	3(P=0.13); I ² =47.09%				
Test for overall effect: Z=6.48(P<0.000	1)				
Total (95% CI)	515	492	-	100%	3.69[2.59,5.26]
Total events: 122 (Treatment), 35 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =21.16, df	=5(P=0); I ² =76.38%				
Test for overall effect: Z=7.22(P<0.000	1)				
Test for subgroup differences: Chi ² =0,	, df=1 (P=0.97), I ² =0%				
	Fa	vours Treatment 0.1	0.2 0.5 1 2 5 10	Favours Control	

Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
6/54	5/56		6.25%	1.27[0.37,4.4]
38/100	40/100	_ _	29.93%	0.92[0.52,1.62]
154	156	-	36.19%	0.97[0.58,1.63]
itrol)				
=1(P=0.64); I ² =0%				
3/27	3/28		3.41%	1.04[0.19,5.59]
9/30	9/30		8.02%	1[0.33,2.99]
2/14	4/14	◀	3.06%	0.44[0.07,2.6]
1/25	3/25	↓	2.35%	0.34[0.05,2.61]
32/46	29/38	+	10.49%	0.72[0.27,1.86]
35/101	32/101		28.17%	1.14[0.64,2.05]
9/35	8/41		8.32%	1.42[0.49,4.17]
278	277	-	63.81%	0.97[0.66,1.44]
itrol)				
=6(P=0.81); I ² =0%				
432	433	•	100%	0.97[0.71.1.33]
ontrol)		Ĩ		
=8(P=0.92): ² =0%				
, df=1 (P=1), I ² =0%				
- · // Fa	vours Treatment	0.1 0.2 0.5 1 2 5	10 Favours Control	
	Treatment n/N 6/54 38/100 154 trol) 1(P=0.64); l ² =0% 3/27 9/30 2/14 1/25 32/46 35/101 9/35 278 trol) c6(P=0.81); l ² =0% 432 ontrol) c8(P=0.92); l ² =0% , df=1 (P=1), l ² =0% Fa	Treatment Control n/N n/N 6/54 5/56 38/100 40/100 154 156 trol) 154 1(P=0.64); l²=0% 3/27 3/27 3/28 9/30 9/30 2/14 4/14 1/25 3/25 32/46 29/38 35/101 32/101 9/35 8/41 278 277 trol) 6(P=0.81); l²=0% 432 433 ontrol) *8(P=0.92); l²=0% , df=1 (P=1), l²=0% Favours Treatment	Treatment Control Peto Odds Ratio n/N n/N Peto, Fixed, 95% Cl $6/54$ $5/56$ $38/100$ $40/100$ 154 156 trol) 154 $1/P = 0.64$); $l^2 = 0\%$ $3/27$ $3/28$ $9/30$ $9/30$ $2/14$ $4/14$ $1/25$ $3/25$ $32/46$ $29/38$ $35/101$ $32/101$ $9/35$ $8/41$ 278 2777 trol) $6(P=0.81); l^2= 0\%$ $6(P=0.92); l^2= 0\%$ 432 $6f=1$ (P=1), l^2= 0\% 1 $far = 10^{-1}$ 1	Treatment Control Peto Odds Ratio Weight n/N n/N Peto, Fixed, 95% Cl 6.25% $6/54$ $5/56$ 6.25% $38/100$ $40/100$ 29.93% 154 156 6.25% 154 156 36.19% 10^{-1} $3/27$ $3/28$ $3/27$ $3/28$ 3.41% $9/30$ $9/30$ $9/30$ $2/14$ $4/14$ 3.06% $1/25$ $3/25$ $3/246$ $29/38$ 277 63.81% $9/35$ $8/41$ 28.17% $9/35$ $8/41$ 8.32% 432 433 63.81% 670 432 433 $61(P=0.91); l^2=0\%$ 100% $61(P=0.92); l^2=0\%$ 10.2 0.5 1 2 5 10

Analysis 11.12. Comparison 11 Subgroup HRT/non HRT, Outcome 12 Withdrawals and dropouts overall.

Analysis 11.13. Comparison 11 Subgroup HRT/non HRT, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control			Peto	Odds R	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
11.13.1 HRT											
Subtotal (95% CI)	0	0									Not estimable
Total events: 0 (Treatment), 0 (Control)											
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
11.13.2 Non HRT											
Christiansen 1980	3/27	3/28				+				14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30				+				35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	←		+					13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41						_		36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	106	113				\blacklozenge	•			100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Contr	ol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, df=3	(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.94)											
	F	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto C)dds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	xed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	106	113				\bullet				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, d	f=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.94	4)										
Test for subgroup differences: Not a	pplicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 11.14. Comparison 11 Subgroup HRT/non HRT, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
11.14.1 HRT					
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100	_	38.78%	0.92[0.52,1.62]
Subtotal (95% CI)	154	156		46.88%	0.97[0.58,1.63]
Total events: 44 (Treatment), 45 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0.22, df=1	(P=0.64); I ² =0%				
Test for overall effect: Z=0.11(P=0.92)					
11.14.2 Non HRT					
Hansson 1987	1/25	3/25	← +	3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	13.58%	0.72[0.27,1.86]
Riggs 1990	35/101	32/101		36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	172	164	-	53.12%	0.95[0.58,1.54]
Total events: 68 (Treatment), 64 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =1.69, df=2	2(P=0.43); I ² =0%				
Test for overall effect: Z=0.22(P=0.82)					
Total (95% CI)	326	320	-	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Chi ² =0.0	01, df=1 (P=0.94), I ² =	0%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Comparison 12. Subgroup SR/non SR

Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. People with new vertebral frac- tures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.13, 0.86]
1.2 Non SR	3	632	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.77, 1.56]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 No. People with new vertebral frac- tures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.11, 0.61]
2.2 Non SR	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.52, 1.27]
3 Lumbar BMD % 2 years from baseline	7	1002	Mean Difference (IV, Fixed, 95% CI)	9.73 [8.82, 10.64]
3.1 SR	1	99	Mean Difference (IV, Fixed, 95% CI)	9.34 [6.00, 12.68]
3.2 Non SR	6	903	Mean Difference (IV, Fixed, 95% CI)	9.76 [8.81, 10.71]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 SR	1	99	Mean Difference (IV, Fixed, 95% CI)	18.68 [11.73, 25.63]
4.2 Non SR	2	402	Mean Difference (IV, Fixed, 95% CI)	14.69 [13.17, 16.20]
5 GI minor overall	9	1145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.15, 2.11]
5.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.34, 5.14]
5.2 Non SR	8	1035	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [1.16, 2.14]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 SR	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Non SR	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
7 GI minor 4 years	4	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [1.87, 5.39]
7.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.34, 5.14]
7.2 Non SR	3	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.71 [2.09, 6.60]
8 Non vertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.15, 2.55]
8.2 Non SR	4	840	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.48, 2.99]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.1 SR	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Non SR	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
10 Non vertebral fractures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.15, 2.55]
10.2 Non SR	3	486	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.69 [1.76, 4.11]
11 Lower limb pain syndrome	6	1007	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.69 [2.59, 5.26]
11.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.25, 2.30]
11.2 Non SR	5	897	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.41 [3.03, 6.41]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
12.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.37, 4.40]
12.2 Non SR	8	755	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.69, 1.32]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 SR	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Non SR	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.37, 4.40]
14.2 Non SR	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.65, 1.35]

Analysis 12.1. Comparison 12 Subgroup SR/non SR, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment	Control	Peto	Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N	Peto,	Fixed, 95% CI			Peto, Fixed, 95% CI
12.1.1 SR							
Pak 1995	6/54	16/56	+	_		12.66%	0.34[0.13,0.86]
Subtotal (95% CI)	54	56		-		12.66%	0.34[0.13,0.86]
Total events: 6 (Treatment), 16 (Contro	ol)						
Heterogeneity: Not applicable							
Test for overall effect: Z=2.28(P=0.02)							
12.1.2 Non SR							
Meunier 1998	69/208	37/146				51.48%	1.45[0.91,2.3]
Riggs 1990	33/101	42/101		•		33.79%	0.68[0.39,1.21]
Sebert 1995	2/35	1/41		· · · ·		2.07%	2.35[0.23,23.42]
	Fa	avours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Fav	ours Control	

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Study or subgroup	Treatment	Control			Peto	Odds F	latio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
Subtotal (95% CI)	344	288				+	•			87.34%	1.1[0.77,1.56]
Total events: 104 (Treatment), 80 (C	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =4.47, df	=2(P=0.11); I ² =55.3%										
Test for overall effect: Z=0.51(P=0.61)										
Total (95% CI)	398	344				\blacklozenge				100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (C	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =9.82, df	=3(P=0.02); I ² =69.44%										
Test for overall effect: Z=0.33(P=0.74)										
Test for subgroup differences: Chi ² =	5.34, df=1 (P=0.02), I ² =8	1.28%									
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 12.2. Comparison 12 Subgroup SR/non SR, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
12.2.1 SR					
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Subtotal (95% CI)	54	56		21.68%	0.26[0.11,0.61]
Total events: 7 (Treatment), 22 (Contre	ol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=3.12(P=0)					
12.2.2 Non SR					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Reginster 1998	1/100	7/100	← →────	7.77%	0.21[0.05,0.87]
Riggs 1990	40/101	45/101	— <u>—</u> —	49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	272	264		78.32%	0.81[0.52,1.27]
Total events: 72 (Treatment), 75 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =6.13, df=3	3(P=0.11); I ² =51.09%				
Test for overall effect: Z=0.91(P=0.36)					
Total (95% CI)	326	320		100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df	=4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Chi ² =5.4	45, df=1 (P=0.02), I ² =81	.65%			

Favours Treatment Favours Control

Analysis 12.3. Comparison 12 Subgroup SR/non SR, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tr	eatment	atment Co		ntrol		Mean Difference			Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)			Fixed, 95% CI				Fixed, 95% CI
12.3.1 SR											
Pak 1995	48	109.6 (10.3)	51	100.3 (6)				_	\rightarrow	7.48%	9.34[6,12.68]
Subtotal ***	48		51					-		7.48%	9.34[6,12.68]
			Favou	irs Treatment	-10	-5	0	5	10	Favours Contro	l

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Study or subgroup	Tre	atment	c	ontrol	Mean Di	ifference	Weight	Mean Difference
	Ν	Mean(SD)	N	Mean(SD)	Fixed,	95% CI	0	Fixed, 95% CI
Heterogeneity: Not applicable								
Test for overall effect: Z=5.48(P<0.000	1)							
12.3.2 Non SR								
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		·	7.99%	6.2[2.97,9.43]
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)			1.18%	12.2[3.78,20.62]
Meunier 1998	146	110.8 (27.4)	208	102.4 (21.1)			2.98%	8.4[3.11,13.69]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)			66.44%	8.04[6.92,9.16]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)			11.74%	21.79[19.12,24.46]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)			2.19%	11.06[4.88,17.24]
Subtotal ***	418		485			▲	92.52%	9.76[8.81,10.71]
Heterogeneity: Tau ² =0; Chi ² =92.63, d	=5(P<0.0	0001); I ² =94.6%						
Test for overall effect: Z=20.14(P<0.00	001)							
Total ***	466		536			•	100%	9.73[8.82,10.64]
Heterogeneity: Tau ² =0; Chi ² =92.68, d	=6(P<0.0	0001); I ² =93.53%						
Test for overall effect: Z=20.87(P<0.00	01)							
Test for subgroup differences: Chi ² =0	.06, df=1	(P=0.81), I ² =0%						
			Favou	urs Treatment	-10 -5	0 5 10	Favours Control	

Analysis 12.4. Comparison 12 Subgroup SR/non SR, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	atment	с	ontrol		Mean D	ifference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fixed	, 95% CI			Fixed, 95% CI
12.4.1 SR										
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)					4.53%	18.68[11.73,25.63]
Subtotal ***	48		51						4.53%	18.68[11.73,25.63]
Heterogeneity: Not applicable										
Test for overall effect: Z=5.27(P<0.000	1)									
12.4.2 Non SR										
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)					81.5%	10.4[8.76,12.04]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)					13.96%	39.73[35.77,43.69]
Subtotal ***	201		201						95.47%	14.69[13.17,16.2]
Heterogeneity: Tau ² =0; Chi ² =179.7, df	=1(P<0.0	0001); I ² =99.44%								
Test for overall effect: Z=19(P<0.0001)										
Total ***	249		252						100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, c	lf=2(P<0	.0001); I ² =98.89%								
Test for overall effect: Z=19.69(P<0.00	01)									
Test for subgroup differences: Chi ² =1.	21, df=1	(P=0.27), I ² =17.23	3%							
			Favou	irs Treatment	-10	-5	0 5	10	Favours Co	ntrol

Analysis 12.5. Comparison 12 Subgroup SR/non SR, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
12.5.1 SR					
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Subtotal (95% CI)	54	56		4.93%	1.32[0.34,5.14]
Total events: 5 (Treatment), 4 (Control	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
12.5.2 Non SR					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14		1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25	│ ─── ►	2.22%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		9.63%	2.64[1,6.97]
Meunier 1998	123/208	87/146	— —	49.11%	0.98[0.64,1.51]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	+	12.57%	2.56[1.09,6]
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	530	505	•	95.07%	1.57[1.16,2.14]
Total events: 188 (Treatment), 116 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =22.56, df=	=7(P=0); I ² =68.97%				
Test for overall effect: Z=2.87(P=0)					
Total (95% CI)	584	561	•	100%	1.56[1.15,2.11]
Total events: 193 (Treatment), 120 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =22.62, df=	=8(P=0); I ² =64.64%				
Test for overall effect: Z=2.89(P=0)					
Test for subgroup differences: Chi ² =0.0	06, df=1 (P=0.81), l ² =0	0%			
-	Fay	vours Treatment 0.1	0.2 0.5 1 2 5 10	Favours Control	

Analysis 12.6. Comparison 12 Subgroup SR/non SR, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
12.6.1 SR					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
12.6.2 Non SR					
Gambacciani 1995	7/30	6/30		9.36%	1.21[0.36,4.1]
Grove 1981	1/14	1/14	•	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146		75.07%	0.98[0.64,1.51]
Sebert 1995	10/45	9/49	+	13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	297	239	•	100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.28, df=3	(P=0.96); I ² =0%				
Test for overall effect: Z=0.19(P=0.85)					
		Favours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	297	239				\blacklozenge	•			100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103	(Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28,	df=3(P=0.96); l ² =0%										
Test for overall effect: Z=0.19(P=0.3	85)										
Test for subgroup differences: Not	applicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 12.7. Comparison 12 Subgroup SR/non SR, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
12.7.1 SR					
Pak 1995	5/54	4/56	+	15.23%	1.32[0.34,5.14]
Subtotal (95% CI)	54	56		15.23%	1.32[0.34,5.14]
Total events: 5 (Treatment), 4 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
12.7.2 Non SR					
Kleerekoper 1991	16/46	6/38		29.76%	2.64[1,6.97]
Riggs 1982	10/61	0/102		16.17%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		38.84%	2.56[1.09,6]
Subtotal (95% CI)	208	241		84.77%	3.71[2.09,6.6]
Total events: 43 (Treatment), 13 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =6.3, df=	2(P=0.04); I ² =68.24%				
Test for overall effect: Z=4.47(P<0.00	01)				
Total (95% CI)	262	297		100%	3.17[1.87,5.39]
Total events: 48 (Treatment), 17 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =8.18, df	=3(P=0.04); I ² =63.33%				
Test for overall effect: Z=4.27(P<0.00	01)				
Test for subgroup differences: Chi ² =:	1.88, df=1 (P=0.17), l ² =4	16.9%			
	Fav	vours Treatment 0.1	0.2 0.5 1 2 5 10	Favours Control	

Analysis 12.8. Comparison 12 Subgroup SR/non SR, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control			Peto O	dds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fiz	xed,	95% CI				Peto, Fixed, 95% CI
12.8.1 SR											
Pak 1995	3/54	5/56	-		+	-				5.69%	0.61[0.15,2.55]
Subtotal (95% CI)	54	56	-							5.69%	0.61[0.15,2.55]
Total events: 3 (Treatment), 5 (Control))										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.68(P=0.5)											
12.8.2 Non SR											
Kleerekoper 1991	13/46	7/38					+	—		11.61%	1.71[0.63,4.66]
	Fa	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds R	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	5% CI				Peto, Fixed, 95% CI
Meunier 1998	29/208	17/146			_					29.56%	1.22[0.65,2.3]
Reginster 1998	12/100	11/100				-+				15.54%	1.1[0.46,2.62]
Riggs 1990	61/101	24/101							-	37.6%	4.46[2.56,7.79]
Subtotal (95% CI)	455	385				-				94.31%	2.1[1.48,2.99]
Total events: 115 (Treatment), 59 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =12.14, c	lf=3(P=0.01); I ² =75.29%)									
Test for overall effect: Z=4.13(P<0.00	01)										
Total (95% CI)	509	441					•			100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (Co	ontrol)										
Heterogeneity: Tau ² =0; Chi ² =14.84, c	lf=4(P=0.01); l ² =73.05%)									
Test for overall effect: Z=3.85(P=0)											
Test for subgroup differences: Chi ² =2	2.7, df=1 (P=0.1), I ² =62.9	99%									
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 12.9. Comparison 12 Subgroup SR/non SR, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Od	ds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% CI
12.9.1 SR						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control)						
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.9.2 Non SR						
Meunier 1998	29/208	17/146			100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146			100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
				-		
Total (95% CI)	208	146			100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
Test for subgroup differences: Not applie	cable					
	F	avours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

Analysis 12.10. Comparison 12 Subgroup SR/non SR, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	, 95% CI				Peto, Fixed, 95% CI
12.10.1 SR											
Pak 1995	3/54	5/56			+					8.07%	0.61[0.15,2.55]
Subtotal (95% CI)	54	56								8.07%	0.61[0.15,2.55]
Total events: 3 (Treatment), 5 (Control	l)										
	Fa	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control								weight	Peto Odds Ratio	
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl	
Heterogeneity: Not applicable												
Test for overall effect: Z=0.68(P=0.5)												
12.10.2 Non SR												
Kleerekoper 1991	13/46	7/38			-		•			16.49%	1.71[0.63,4.66	6]
Reginster 1998	12/100	11/100				-				22.07%	1.1[0.46,2.62	2]
Riggs 1990	61/101	24/101					_	-	-	53.37%	4.46[2.56,7.79	Э]
Subtotal (95% CI)	247	239						►		91.93%	2.69[1.76,4.11	L]
Total events: 86 (Treatment), 42 (Con	itrol)											
Heterogeneity: Tau ² =0; Chi ² =8.02, df=	=2(P=0.02); I ² =75.07%											
Test for overall effect: Z=4.56(P<0.000	01)											
Total (95% CI)	301	295					\blacklozenge	•		100%	2.38[1.59,3.58	3]
Total events: 89 (Treatment), 47 (Con	itrol)											
Heterogeneity: Tau ² =0; Chi ² =11.81, d	f=3(P=0.01); I ² =74.59%											
Test for overall effect: Z=4.18(P<0.000	01)											
Test for subgroup differences: Chi ² =3	.79, df=1 (P=0.05), I ² =73.	58%										
	Favo	urs Treatment	0.1	0.2	0.5	1	2	5	10	Eavours Control		

Favours Treatment Favours Control

Analysis 12.11. Comparison 12 Subgroup SR/non SR, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
12.11.1 SR					
Pak 1995	6/54	8/56	+	10.07%	0.75[0.25,2.3]
Subtotal (95% CI)	54	56		10.07%	0.75[0.25,2.3]
Total events: 6 (Treatment), 8 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					
12.11.2 Non SR					
Kleerekoper 1991	23/46	13/38	+ +	16.85%	1.89[0.8,4.48]
Meunier 1998	37/208	7/146	_	30.59%	3.29[1.73,6.24]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101		27.3%	6.78[3.44,13.36]
Sebert 1995	5/45	2/49		5.34%	2.74[0.59,12.71]
Subtotal (95% CI)	461	436	•	89.93%	4.41[3.03,6.41]
Total events: 116 (Treatment), 27 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =12.51, df=	4(P=0.01); I ² =68.049	6			
Test for overall effect: Z=7.78(P<0.0001)				
Total (95% CI)	515	492	•	100%	3.69[2.59,5.26]
Total events: 122 (Treatment), 35 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =21.16, df=	5(P=0); I ² =76.38%				
Test for overall effect: Z=7.22(P<0.0001)				
Test for subgroup differences: Chi ² =8.6	5, df=1 (P=0), I ² =88.	44%			
	Fa	vours Treatment ^{0.}	1 0.2 0.5 1 2 5 10	Favours Control	

Study or subgroup	Treatment	Control		Peto Odds Rat	io	Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95%	% CI		Peto, Fixed, 95% CI
12.12.1 SR							
Pak 1995	6/54	5/56				6.25%	1.27[0.37,4.4]
Subtotal (95% CI)	54	56				6.25%	1.27[0.37,4.4]
Total events: 6 (Treatment), 5 (Cont	rol)						
Heterogeneity: Not applicable							
Test for overall effect: Z=0.38(P=0.7)							
12.12.2 Non SR	- /	- /					
Christiansen 1980	3/27	3/28		1		3.41%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30				8.02%	1[0.33,2.99]
Grove 1981	2/14	4/14				3.06%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25	◀	+		2.35%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38		+		10.49%	0.72[0.27,1.86]
Reginster 1998	38/100	40/100				29.93%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101			-	28.17%	1.14[0.64,2.05]
Sebert 1995	9/35	8/41				8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	378	377		•		93.75%	0.96[0.69,1.32]
Total events: 129 (Treatment), 128 (Control)						
Heterogeneity: Tau ² =0; Chi ² =2.98, d	f=7(P=0.89); I ² =0%						
Test for overall effect: Z=0.27(P=0.78	3)						
Total (95% CI)	432	433		•		100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133 (Control)						. , .
Heterogeneity: Tau ² =0; Chi ² =3.17. d	, f=8(P=0.92); I ² =0%						
Test for overall effect: Z=0.17(P=0.86	5)						
Test for subgroup differences: Chi ² =	0 19 df=1 (P=0 66) l ² =	0%					
			0.1 0.2	0.5 1	2 5 1/		
	Fa	vours Treatment	0.1 0.2	0.5 1	2 5 10	Pavours Control	

Analysis 12.12. Comparison 12 Subgroup SR/non SR, Outcome 12 Withdrawals and dropouts overall.

Analysis 12.13. Comparison 12 Subgroup SR/non SR, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control	Peto Od	lds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% CI
12.13.1 SR						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.13.2 Non SR						
Christiansen 1980	3/27	3/28		•	14.94%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30			35.17%	1[0.33,2.99]
Grove 1981	2/14	4/14	+		13.42%	0.44[0.07,2.6]
Sebert 1995	9/35	8/41			36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	106	113			100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Contr	rol)					
Heterogeneity: Tau ² =0; Chi ² =1.23, df=3	(P=0.75); I ² =0%					
Test for overall effect: Z=0.07(P=0.94)						
	ļ	Favours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds I	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	106	113				\blacklozenge				100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =1.23, df	=3(P=0.75); I ² =0%										
Test for overall effect: Z=0.07(P=0.94)										
Test for subgroup differences: Not a	oplicable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 12.14. Comparison 12 Subgroup SR/non SR, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
12.14.1 SR					
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Subtotal (95% CI)	54	56		8.1%	1.27[0.37,4.4]
Total events: 6 (Treatment), 5 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					
12.14.2 Non SR					
Hansson 1987	1/25	3/25		3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	+	13.58%	0.72[0.27,1.86]
Reginster 1998	38/100	40/100		38.78%	0.92[0.52,1.62]
Riggs 1990	35/101	32/101		36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	272	264	-	91.9%	0.93[0.65,1.35]
Total events: 106 (Treatment), 104 (Control)				
Heterogeneity: Tau ² =0; Chi ² =1.69, df	f=3(P=0.64); I ² =0%				
Test for overall effect: Z=0.36(P=0.72	2)				
Total (95% CI)	326	320	-	100%	0.96[0.67,1.36]
Total events: 112 (Treatment), 109 (Control)				
Heterogeneity: Tau ² =0; Chi ² =1.91, df	f=4(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81	.)				
Test for subgroup differences: Chi ² =	0.22, df=1 (P=0.64), I ² =0	0%		1	
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 1	¹⁰ Favours Control	

Comparison 13. Subgroup Ca dosage and/or vit D

Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 No. people with new vertebral fracture 2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 Ca 500	2	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.19, 1.05]
1.2 Ca 1000	1	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.39, 1.21]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.3 Ca and vit D	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.91, 2.30]
2 No. people with new vertebral fracture 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 Ca 500	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.12, 0.51]
2.2 Ca 1000	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.59, 1.51]
2.3 Ca and vit D	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Lumbar BMD % 2 years from baseline	6	648	Mean Difference (IV, Fixed, 95% CI)	9.77 [8.84, 10.70]
3.1 Ca 500	4	400	Mean Difference (IV, Fixed, 95% CI)	8.06 [7.06, 9.06]
3.2 Ca 1000	2	248	Mean Difference (IV, Fixed, 95% CI)	20.92 [18.37, 23.46]
3.3 Ca and vit D	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Lumbar BMD % 4 years from baseline	3	501	Mean Difference (IV, Fixed, 95% CI)	14.87 [13.39, 16.35]
4.1 Ca 500	2	299	Mean Difference (IV, Fixed, 95% CI)	10.84 [9.24, 12.43]
4.2 Ca 1000	1	202	Mean Difference (IV, Fixed, 95% CI)	39.73 [35.77, 43.69]
4.3 Ca and vit D	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 GI minor overall	7	932	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.96, 1.79]
5.1 Ca 500	3	264	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.64, 2.47]
5.2 Ca 1000	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.37, 4.92]
5.3 Ca and vit D	2	382	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.64, 1.50]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 Ca 500	2	154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.57, 2.70]
6.2 Ca 1000	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Ca and vit D	2	382	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.64, 1.50]
7 GI minor 4 years	3	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [1.29, 4.10]
7.1 Ca 500	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.34, 5.14]
7.2 Ca 1000	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.60 [1.37, 4.92]
7.3 Ca and vit D	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
8 Non vertebral frac- tures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 Ca 500	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.15, 2.55]
8.2 Ca 1000	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.56 [2.19, 5.79]
8.3 Ca and vit D	2	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.71, 1.96]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.1 Ca 500	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Ca 1000	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Ca and vit D	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
10 Non vertebral frac- tures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 Ca 500	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.45, 1.97]
10.2 Ca 1000	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.56 [2.19, 5.79]
10.3 Ca and vit D	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Lower limb pain syndrome	5	844	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.10 [2.13, 4.50]
11.1 Ca 500	2	204	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.48, 2.91]
11.2 Ca 1000	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.17 [2.44, 7.10]
11.3 Ca and vit D	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.29 [1.73, 6.24]
12 Withdrawals and dropouts overall	9	865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.33]
12.1 Ca 500	4	446	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.68, 1.59]
12.2 Ca 1000	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.58, 1.54]
12.3 Ca and vit D	2	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.20, 2.35]
13 Withdrawals and dropouts 2 years	4	219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.54, 1.96]
13.1 Ca 500	2	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.56, 2.58]
13.2 Ca 1000	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Ca and vit D	2	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.20, 2.35]

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Outcome or sub- group title	No. of studies	No. of partici- pants	Statistical method	Effect size
14 Withdrawals and dropouts 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.67, 1.36]
14.1 Ca 500	2	310	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.58, 1.63]
14.2 Ca 1000	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.58, 1.54]
14.3 Ca and vit D	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 13.1. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 1 No. people with new vertebral fracture 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
13.1.1 Ca 500					
Pak 1995	6/54	16/56		12.66%	0.34[0.13,0.86]
Sebert 1995	2/35	1/41		2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	89	97		14.73%	0.44[0.19,1.05]
Total events: 8 (Treatment), 17 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =2.33, df=1	(P=0.13); I ² =57.12%				
Test for overall effect: Z=1.84(P=0.07)					
13.1.2 Ca 1000					
Riggs 1990	33/101	42/101		33.79%	0.68[0.39,1.21]
Subtotal (95% CI)	101	101		33.79%	0.68[0.39,1.21]
Total events: 33 (Treatment), 42 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
13.1.3 Ca and vit D					
Meunier 1998	69/208	37/146		51.48%	1.45[0.91,2.3]
Subtotal (95% CI)	208	146		51.48%	1.45[0.91,2.3]
Total events: 69 (Treatment), 37 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.58(P=0.11)					
Total (95% CI)	398	344	•	100%	0.95[0.68,1.32]
Total events: 110 (Treatment), 96 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =9.82, df=3	(P=0.02); I ² =69.44%				
Test for overall effect: Z=0.33(P=0.74)					
Test for subgroup differences: Chi ² =7.4	9, df=1 (P=0.02), I ² =	73.28%			
	Fa	vours Treatment 0	0.1 0.2 0.5 1 2 5 10	Favours Control	

Analysis 13.2. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 2 No. people with new vertebral fracture 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
13.2.1 Ca 500					
Pak 1995	7/54	22/56		21.68%	0.26[0.11,0.61]
Reginster 1998	1/100	7/100	↓ →	7.77%	0.21[0.05,0.87]
Subtotal (95% CI)	154	156		29.45%	0.25[0.12,0.51]
Total events: 8 (Treatment), 29 (Contro	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.06, df=1	(P=0.8); I ² =0%				
Test for overall effect: Z=3.78(P=0)					
13.2.2 Ca 1000					
Hansson 1987	0/25	1/25	↓	1.01%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		19.74%	1.5[0.62,3.63]
Riggs 1990	40/101	45/101		49.8%	0.82[0.47,1.43]
Subtotal (95% CI)	172	164	-	70.55%	0.94[0.59,1.51]
Total events: 71 (Treatment), 68 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =2.24, df=2	(P=0.33); I ² =10.79%				
Test for overall effect: Z=0.24(P=0.81)					
13.2.3 Ca and vit D					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	326	320	-	100%	0.64[0.43,0.94]
Total events: 79 (Treatment), 97 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =11.58, df=	4(P=0.02); I ² =65.47%				
Test for overall effect: Z=2.26(P=0.02)					
Test for subgroup differences: Chi ² =9.2	8, df=1 (P=0), I ² =89.22	2%			
	Favo	ours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 13.3. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Tre	atment	Control		Mean Difference		Weight	Mean Difference	
	N	Mean(SD)	Ν	Mean(SD)		Fixed,	95% CI		Fixed, 95% CI
13.3.1 Ca 500									
Pak 1995	48	109.6 (10.3)	51	100.3 (6)				7.71%	9.34[6,12.68]
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)			+	8.24%	6.2[2.97,9.43]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)				68.48%	8.04[6.92,9.16]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)			>	2.25%	11.06[4.88,17.24]
Subtotal ***	195		205				•	86.68%	8.06[7.06,9.06]
Heterogeneity: Tau ² =0; Chi ² =2.74, df=	3(P=0.43	3); I ² =0%							
Test for overall effect: Z=15.85(P<0.00	01)								
13.3.2 Ca 1000									
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)			>	1.21%	12.2[3.78,20.62]
Riggs 1990	101	121.8 (11.4)	101	100 (7.6)				12.11%	21.79[19.12,24.46]
Subtotal ***	125		123					13.32%	20.92[18.37,23.46]
			Favou	urs Treatment	-10 -5	() 5 10	Favours Co	ntrol

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Study or subgroup	Tre	Treatment		Control		Me	an Difference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		Fi	xed, 95% CI		-	Fixed, 95% CI
Heterogeneity: Tau ² =0; Chi ² =4.52, df	=1(P=0.0	3); I ² =77.9%								
Test for overall effect: Z=16.13(P<0.0	001)									
13.3.3 Ca and vit D										
Subtotal ***	0		0							Not estimable
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
Total ***	320		328					-	100%	9.77[8.84,10.7]
Heterogeneity: Tau ² =0; Chi ² =92.43, d	f=5(P<0.	0001); l ² =94.59%								
Test for overall effect: Z=20.64(P<0.0	001)									
Test for subgroup differences: Chi ² =8	5.17, df=	1 (P<0.0001), I ² =9	8.83%							
			Favo	urs Treatment	-10	-5	0 5	10	Favours Contro	

Analysis 13.4. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Tre	atment	ent Cont		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% Cl		Fixed, 95% CI
13.4.1 Ca 500							
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)		4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)		81.5%	10.4[8.76,12.04]
Subtotal ***	148		151			◀ 86.04%	10.84[9.24,12.43]
Heterogeneity: Tau ² =0; Chi ² =5.16, df=	1(P=0.02	2); I ² =80.62%					
Test for overall effect: Z=13.31(P<0.00	01)						
13.4.2 Ca 1000							
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)		13.96%	39.73[35.77,43.69]
Subtotal ***	101		101			13.96%	39.73[35.77,43.69]
Heterogeneity: Not applicable							
Test for overall effect: Z=19.65(P<0.00	01)						
13.4.3 Ca and vit D							
Subtotal ***	0		0				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	249		252			100%	14.87[13.39,16.35]
Heterogeneity: Tau ² =0; Chi ² =180.91, d	f=2(P<0	.0001); I ² =98.89%					
Test for overall effect: Z=19.69(P<0.00	01)						
Test for subgroup differences: Chi ² =17	5.75, df	=1 (P<0.0001), I ² =	99.43%				
			Favou	urs Treatment	-10 -5 0 5	¹⁰ Favours Cor	ntrol

Analysis 13.5. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 5 GI minor overall.

Study or subgroup	Treatment n/N	Control n/N			Peto Peto, F	Odds ixed,	Ratio 95% CI			Weight	Peto Odds Ratio Peto, Fixed, 95% CI
13.5.1 Ca 500											
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
Gambacciani 1995	7/30	6/30	+	6.62%	1.21[0.36,4.1]
Pak 1995	5/54	4/56	+	5.33%	1.32[0.34,5.14]
Sebert 1995	10/45	9/49		9.77%	1.27[0.46,3.45]
Subtotal (95% CI)	129	135		21.72%	1.26[0.64,2.47]
Total events: 22 (Treatment), 19	(Control)				
Heterogeneity: Tau ² =0; Chi ² =0.01	l, df=2(P=1); l ² =0%				
Test for overall effect: Z=0.68(P=0	0.5)				
13.5.2 Ca 1000					
Kleerekoper 1991	16/46	6/38	+	10.41%	2.64[1,6.97]
Riggs 1990	17/101	7/101		13.58%	2.56[1.09,6]
Subtotal (95% CI)	147	139		23.99%	2.6[1.37,4.92]
Total events: 33 (Treatment), 13	(Control)				
Heterogeneity: Tau ² =0; Chi ² =0, d	f=1(P=0.96); I ² =0%				
Test for overall effect: Z=2.92(P=0))				
13.5.3 Ca and vit D					
Grove 1981	1/14	1/14	•	1.23%	1[0.06,16.85]
Meunier 1998	123/208	87/146		53.06%	0.98[0.64,1.51]
Subtotal (95% CI)	222	160		54.29%	0.98[0.64,1.5]
Total events: 124 (Treatment), 88	3 (Control)				
Heterogeneity: Tau ² =0; Chi ² =0, d	f=1(P=0.99); I ² =0%				
Test for overall effect: Z=0.08(P=0	0.93)				
Total (95% CI)	498	434	•	100%	1.31[0.96,1.79]
Total events: 179 (Treatment), 12	20 (Control)				
Heterogeneity: Tau ² =0; Chi ² =6.18	3, df=6(P=0.4); l ² =2.88%				
Test for overall effect: Z=1.69(P=0	0.09)				
Test for subgroup differences: Ch	ni²=6.17, df=1 (P=0.05), l²=	67.57%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 13.6. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control			Peto (Odds Ra	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	ixed, 9	5% CI				Peto, Fixed, 95% CI
13.6.1 Ca 500											
Gambacciani 1995	7/30	6/30				+•		-		9.36%	1.21[0.36,4.1]
Sebert 1995	10/45	9/49				++				13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	75	79			-					23.19%	1.24[0.57,2.7]
Total events: 17 (Treatment), 15 (Cont	trol)										
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.96); I ² =0%										
Test for overall effect: Z=0.55(P=0.58)											
13.6.2 Ca 1000											
Subtotal (95% CI)	0	0				ĺ					Not estimable
Total events: 0 (Treatment), 0 (Contro	l)					İ					
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
	Fa	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control			Peto C)dds R	atio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, Fi	xed, 9	5% CI				Peto, Fixed, 95% Cl
13.6.3 Ca and vit D											
Grove 1981	1/14	1/14	←						→	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146				-				75.07%	0.98[0.64,1.51]
Subtotal (95% CI)	222	160			-	\blacklozenge				76.81%	0.98[0.64,1.5]
Total events: 124 (Treatment), 88 (C	Control)										
Heterogeneity: Tau ² =0; Chi ² =0, df=1	.(P=0.99); I ² =0%										
Test for overall effect: Z=0.08(P=0.93	3)										
Total (95% CI)	297	239			-	\blacklozenge				100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 ((Control)										
Heterogeneity: Tau ² =0; Chi ² =0.28, d	f=3(P=0.96); I ² =0%										
Test for overall effect: Z=0.19(P=0.8	5)										
Test for subgroup differences: Chi ² =	=0.28, df=1 (P=0.6), I ² =00	%									
	Fav	ours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 13.7. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Od	ds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% CI
13.7.1 Ca 500						
Pak 1995	5/54	4/56		•	18.17%	1.32[0.34,5.14]
Subtotal (95% CI)	54	56			18.17%	1.32[0.34,5.14]
Total events: 5 (Treatment), 4 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.4(P=0.69)						
13.7.2 Ca 1000						
Kleerekoper 1991	16/46	6/38			35.5%	2.64[1,6.97]
Riggs 1990	17/101	7/101		-	46.33%	2.56[1.09,6]
Subtotal (95% CI)	147	139			81.83%	2.6[1.37,4.92]
Total events: 33 (Treatment), 13 (Cont	trol)					
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.96); I ² =0%					
Test for overall effect: Z=2.92(P=0)						
13.7.3 Ca and vit D						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)	201	195			100%	2.3[1.29,4.1]
Total events: 38 (Treatment), 17 (Cont	trol)					
Heterogeneity: Tau ² =0; Chi ² =0.78, df=	2(P=0.68); I ² =0%					
Test for overall effect: Z=2.82(P=0)						
Test for subgroup differences: Chi ² =0.	78, df=1 (P=0.38), I	2=0%				
		Favours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

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Analysis 13.8. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
13.8.1 Ca 500					
Pak 1995	3/54	5/56	+	5.69%	0.61[0.15,2.55]
Subtotal (95% CI)	54	56		5.69%	0.61[0.15,2.55]
Total events: 3 (Treatment), 5 (Cont	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
13.8.2 Ca 1000					
Kleerekoper 1991	13/46	7/38		11.61%	1.71[0.63.4.66]
Riggs 1990	61/101	24/101	i	37.6%	4.46[2.56.7.79]
Subtotal (95% CI)	147	139		49.21%	3.56[2.19,5.79]
Total events: 74 (Treatment), 31 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =2.69, d	f=1(P=0.1); I ² =62.8%				
Test for overall effect: Z=5.11(P<0.00	001)				
13.8.3 Ca and vit D					
Meunier 1998	29/208	17/146		29.56%	1.22[0.65,2.3]
Reginster 1998	12/100	11/100		15.54%	1.1[0.46,2.62]
Subtotal (95% CI)	308	246		45.11%	1.18[0.71,1.96]
Total events: 41 (Treatment), 28 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.04, d	f=1(P=0.85); I ² =0%				
Test for overall effect: Z=0.64(P=0.52	2)				
Total (95% CI)	509	441	-	100%	1.96[1.39,2.75]
Total events: 118 (Treatment), 64 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =14.84, o	df=4(P=0.01); I ² =73.05%	þ			
Test for overall effect: Z=3.85(P=0)					
Test for subgroup differences: Chi ² =	12.12, df=1 (P=0), I ² =83	.49%		1	
	Fay	Jours Treatment 0	.1 0.2 0.5 1 2 5	10 Favours Control	

Favours Treatment Favours Control

Analysis 13.9. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment	Control	Peto Od	lds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fix	ed, 95% CI		Peto, Fixed, 95% CI
13.9.1 Ca 500						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control))					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.9.2 Ca 1000						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control))					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.9.3 Ca and vit D						
Meunier 1998	29/208	17/146			100%	1.22[0.65,2.3]
		Favours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	Fixed,	95% CI				Peto, Fixed, 95% Cl
Subtotal (95% CI)	208	146			-					100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contr	rol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.63(P=0.53)											
Total (95% CI)	208	146			-					100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contr	rol)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.63(P=0.53)											
Test for subgroup differences: Not app	licable										
		Favours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 13.10. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
13.10.1 Ca 500					
Pak 1995	3/54	5/56		8.07%	0.61[0.15,2.55]
Reginster 1998	12/100	11/100		22.07%	1.1[0.46,2.62]
Subtotal (95% CI)	154	156		30.14%	0.94[0.45,1.97]
Total events: 15 (Treatment), 16 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.48, df=1	(P=0.49); I ² =0%				
Test for overall effect: Z=0.16(P=0.87)					
13.10.2 Ca 1000					
Kleerekoper 1991	13/46	7/38		16.49%	1.71[0.63,4.66]
Riggs 1990	61/101	24/101		53.37%	4.46[2.56,7.79]
Subtotal (95% CI)	147	139	-	69.86%	3.56[2.19,5.79]
Total events: 74 (Treatment), 31 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =2.69, df=1	(P=0.1); I ² =62.8%				
Test for overall effect: Z=5.11(P<0.0001)				
13.10.3 Ca and vit D					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)	1				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	301	295	•	100%	2.38[1.59,3.58]
Total events: 89 (Treatment), 47 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =11.81, df=	3(P=0.01); I ² =74.59%	6			
Test for overall effect: Z=4.18(P<0.0001)				
Test for subgroup differences: Chi ² =8.6	4, df=1 (P=0), I ² =88.	42%			
	Fa	vours Treatment 0.1	0.2 0.5 1 2 5 1	¹ Favours Control	

Analysis 13.11. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
13.11.1 Ca 500					
Pak 1995	6/54	8/56	+	11.17%	0.75[0.25,2.3]
Sebert 1995	5/45	2/49		5.92%	2.74[0.59,12.71]
Subtotal (95% CI)	99	105		17.09%	1.18[0.48,2.91]
Total events: 11 (Treatment), 10 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =1.78, df=	=1(P=0.18); I ² =43.92%				
Test for overall effect: Z=0.36(P=0.72)					
13.11.2 Ca 1000					
Kleerekoper 1991	23/46	13/38	+-+	18.69%	1.89[0.8,4.48]
Riggs 1990	37/101	5/101		30.29%	6.78[3.44,13.36]
Subtotal (95% CI)	147	139		48.98%	4.17[2.44,7.1]
Total events: 60 (Treatment), 18 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =5.2, df=1	(P=0.02); I ² =80.78%				
Test for overall effect: Z=5.25(P<0.000	01)				
13.11.3 Ca and vit D					
Meunier 1998	37/208	7/146	_	33.93%	3.29[1.73,6.24]
Subtotal (95% CI)	208	146		33.93%	3.29[1.73,6.24]
Total events: 37 (Treatment), 7 (Cont	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=3.64(P=0)					
Total (95% CI)	454	390	•	100%	3.1[2.13,4.5]
Total events: 108 (Treatment), 35 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =12.61, d	f=4(P=0.01); I ² =68.27%	b			
Test for overall effect: Z=5.94(P<0.000	01)				
Test for subgroup differences: Chi ² =5	.62, df=1 (P=0.06), l ² =6	54.42%			
	Fai	vours Treatment	1 02 05 1 2 5 10	Favours Control	

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 13.12. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 12 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control		Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N		Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
13.12.1 Ca 500						
Gambacciani 1995	9/30	9/30			8.02%	1[0.33,2.99]
Pak 1995	6/54	5/56		+	- 6.25%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100		_	29.93%	0.92[0.52,1.62]
Sebert 1995	9/35	8/41		+	- 8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	219	227		+	52.53%	1.04[0.68,1.59]
Total events: 62 (Treatment), 62 (Con	trol)					
Heterogeneity: Tau ² =0; Chi ² =0.61, df=	3(P=0.89); I ² =0%					
Test for overall effect: Z=0.17(P=0.87)						
13.12.2 Ca 1000						
Hansson 1987	1/25	3/25	←		2.35%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38		+	10.49%	0.72[0.27,1.86]
Riggs 1990	35/101	32/101			28.17%	1.14[0.64,2.05]
	F	avours Treatment	0.1 0	.2 0.5 1 2	⁵ ¹⁰ Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Subtotal (95% CI)	172	164	-	41.01%	0.95[0.58,1.54]
Total events: 68 (Treatment), 64 (C	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =1.69,	df=2(P=0.43); I ² =0%				
Test for overall effect: Z=0.22(P=0.8	32)				
13.12.3 Ca and vit D					
Christiansen 1980	3/27	3/28		3.41%	1.04[0.19,5.59]
Grove 1981	2/14	4/14	┥───	3.06%	0.44[0.07,2.6]
Subtotal (95% CI)	41	42		6.47%	0.69[0.2,2.35]
Total events: 5 (Treatment), 7 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =0.47,	df=1(P=0.49); I ² =0%				
Test for overall effect: Z=0.59(P=0.5	56)				
Total (95% CI)	432	433	+	100%	0.97[0.71,1.33]
Total events: 135 (Treatment), 133	(Control)				
Heterogeneity: Tau ² =0; Chi ² =3.17,	df=8(P=0.92); I ² =0%				
Test for overall effect: Z=0.17(P=0.8	36)				
Test for subgroup differences: Chi ²	=0.4, df=1 (P=0.82), I ² =0	%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2	⁵ ¹⁰ Favours Control	

Analysis 13.13. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control			Peto Odo	ds Ratio			Weight	Peto Odds Ratio
	n/N	n/N		Р	eto, Fixe	d, 95% (:			Peto, Fixed, 95% CI
13.13.1 Ca 500										
Gambacciani 1995	9/30	9/30		_			_		35.17%	1[0.33,2.99]
Sebert 1995	9/35	8/41				-			36.48%	1.42[0.49,4.17]
Subtotal (95% CI)	65	71							71.64%	1.2[0.56,2.58]
Total events: 18 (Treatment), 17 (Contr	ol)									
Heterogeneity: Tau ² =0; Chi ² =0.2, df=1(F	P=0.65); I ² =0%									
Test for overall effect: Z=0.46(P=0.65)										
13.13.2 Ca 1000										
Subtotal (95% CI)	0	0								Not estimable
Total events: 0 (Treatment), 0 (Control)	1									
Heterogeneity: Not applicable										
Test for overall effect: Not applicable										
13.13.3 Ca and vit D										
Christiansen 1980	3/27	3/28			-				14.94%	1.04[0.19,5.59]
Grove 1981	2/14	4/14	←		•		-		13.42%	0.44[0.07,2.6]
Subtotal (95% CI)	41	42							28.36%	0.69[0.2,2.35]
Total events: 5 (Treatment), 7 (Control)	1									
Heterogeneity: Tau ² =0; Chi ² =0.47, df=1	(P=0.49); I ² =0%									
Test for overall effect: Z=0.59(P=0.56)										
Total (95% CI)	106	113							100%	1.03[0.54,1.96]
Total events: 23 (Treatment), 24 (Contr	ol)									
Heterogeneity: Tau ² =0; Chi ² =1.23, df=3	(P=0.75); I ² =0%		_			,		,		
	Fa	avours Treatment	0.1	0.2	0.5 1	2	5	10	Favours Control	

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Study or subgroup	Treatment n/N	Control n/N			Peto (Peto, F	Odds ixed,	Ratio 95% Cl			Weight	Peto Odds Ratio Peto, Fixed, 95% Cl
Test for overall effect: Z=0.07(P=0.94)											
Test for subgroup differences: Chi ² =0.	.55, df=1 (P=0.46), I ² =	-0%					1				
	Fa	avours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 13.14. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
13.14.1 Ca 500					
Pak 1995	6/54	5/56		8.1%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100	_ _	38.78%	0.92[0.52,1.62]
Subtotal (95% CI)	154	156	-	46.88%	0.97[0.58,1.63]
Total events: 44 (Treatment), 45 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =0.22, df=1	(P=0.64); I ² =0%				
Test for overall effect: Z=0.11(P=0.92)					
13.14.2 Ca 1000					
Hansson 1987	1/25	3/25	↓	3.05%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38	· · · · · · · · · · · · · · · · · · ·	13.58%	0.72[0.27,1.86]
Riggs 1990	35/101	32/101	_	36.49%	1.14[0.64,2.05]
Subtotal (95% CI)	172	164	-	53.12%	0.95[0.58,1.54]
Total events: 68 (Treatment), 64 (Contr	ol)				
Heterogeneity: Tau ² =0; Chi ² =1.69, df=2	(P=0.43); I ² =0%				
Test for overall effect: Z=0.22(P=0.82)					
13.14.3 Ca and vit D					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control))				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	326	320	•	100%	0.96[0.67.1.36]
Total events: 112 (Treatment), 109 (Cor	ntrol)				- / -
Heterogeneity: Tau ² =0; Chi ² =1.91, df=4	(P=0.75); I ² =0%				
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Chi ² =0.0	1, df=1 (P=0.94), I ² =	0%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Comparison 14. Subgroup Osteoporosis definition

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size	
1 No. People with new vertebral fractures - 2 years	4	1054	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.61, 1.06]	
1.1 Incident fractures	3	666	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.66, 1.30]	

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.2 BMD	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [0.23, 23.42]
1.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.35, 0.92]
2 No. People with new vertebral fractures - 4 years	5	958	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.45, 0.82]
2.1 Incident fractures	4	446	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.46, 1.05]
2.2 BMD	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.05, 0.87]
2.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.36, 0.92]
3 Lumbar BMD % from baseline 2 years	7	1207	Mean Difference (IV, Fixed, 95% CI)	11.80 [11.02, 12.59]
3.1 incident fractures	4	606	Mean Difference (IV, Fixed, 95% CI)	16.19 [14.58, 17.81]
3.2 BMD	3	301	Mean Difference (IV, Fixed, 95% CI)	7.93 [6.89, 8.98]
3.3 Fractures or BMD	2	300	Mean Difference (IV, Fixed, 95% CI)	17.64 [15.87, 19.41]
4 Lumbar BMD % from baseline 4 years	3	800	Mean Difference (IV, Fixed, 95% CI)	19.48 [18.20, 20.76]
4.1 Incident fractures	2	300	Mean Difference (IV, Fixed, 95% CI)	33.73 [30.82, 36.63]
4.2 BMD	1	200	Mean Difference (IV, Fixed, 95% CI)	10.40 [8.76, 12.04]
4.3 Fractures or BMD	2	300	Mean Difference (IV, Fixed, 95% CI)	33.73 [30.82, 36.63]
5 GI minor overall	9	1620	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [1.38, 2.37]
5.1 Incident fractures	7	991	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [1.17, 2.25]
5.2 BMD	2	154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.57, 2.70]
5.3 Fractures or BMD	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [1.82, 6.45]
6 GI minor 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 Incident fractures	2	382	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.64, 1.50]
6.2 BMD	2	154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.57, 2.70]
6.3 Fractures or BMD	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 GI minor 4 years	4	1034	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.28 [2.18, 4.92]
7.1 Incident fractures	4	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [1.87, 5.39]
7.2 BMD	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
7.3 Fractures or BMD	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [1.82, 6.45]
8 Non vertebral frac- tures overall	5	1262	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [1.74, 3.09]
8.1 Incident fractures	4	750	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.50, 3.15]
8.2 BMD	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.46, 2.62]
8.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [2.04, 5.77]
9 Non vertebral frac- tures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.1 Incident fractures	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
9.2 BMD	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Fractures or BMD	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Non vertebral frac- tures 4 years	4	908	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [1.99, 3.77]
10.1 Incident fractures	3	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.96 [1.87, 4.70]
10.2 BMD	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.46, 2.62]
10.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [2.04, 5.77]
11 Lower limb pain syn- drome	6	1482	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.12 [3.08, 5.52]
11.1 BMD	5	913	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.75 [2.61, 5.40]
11.2 BMD	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [0.59, 12.71]
11.3 Fractures or BMD	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.22 [3.12, 8.74]
12 Withdrawals and dropouts overall	8	1122	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.78, 1.34]
12.1 Incident fractures	5	474	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.61, 1.45]
12.2 BMD	3	336	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.64, 1.59]
12.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.69, 1.98]
13 Withdrawals and dropouts 2 years	3	164	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.51, 2.07]
13.1 Incident fractures	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.07, 2.60]
13.2 BMD	2	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.56, 2.58]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
13.3 Fractures or BMD	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals and dropouts 4 years	4	874	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.78, 1.44]
14.1 Incident fractures	3	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.65, 1.80]
14.2 BMD	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.52, 1.62]
14.3 Fractures or BMD	2	312	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.69, 1.98]

Analysis 14.1. Comparison 14 Subgroup Osteoporosis definition, Outcome 1 No. People with new vertebral fractures - 2 years.

Study or subgroup Favours Fluoride		Favours Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
14.1.1 Incident fractures					
Meunier 1998	69/208	37/146	+ 	35.15%	1.45[0.91,2.3]
Pak 1995	6/54	16/56		8.65%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		23.07%	0.68[0.39,1.21]
Subtotal (95% CI)	363	303	•	66.87%	0.93[0.66,1.3]
Total events: 108 (Favours Fluoride),	95 (Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =9.21, df=	2(P=0.01); I ² =78.28%				
Test for overall effect: Z=0.44(P=0.66)					
14.1.2 BMD					
Sebert 1995	2/35	1/41		1.41%	2.35[0.23,23.42]
Subtotal (95% CI)	35	41		1.41%	2.35[0.23,23.42]
Total events: 2 (Favours Fluoride), 1 (Favours Placebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
14.1.3 Fractures or BMD					
Pak 1995	6/54	16/56		8.65%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		23.07%	0.68[0.39,1.21]
Subtotal (95% CI)	155	157		31.72%	0.56[0.35,0.92]
Total events: 39 (Favours Fluoride), 5	8 (Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1.59, df=	1(P=0.21); I ² =37.07%				
Test for overall effect: Z=2.3(P=0.02)					
Total (95% CI)	553	501	•	100%	0.8[0.61,1.06]
Total events: 149 (Favours Fluoride),	154 (Favours Placebo)			
Heterogeneity: Tau ² =0; Chi ² =14.36, d	f=5(P=0.01); I ² =65.17%	b			
Test for overall effect: Z=1.57(P=0.12)					
Test for subgroup differences: Chi ² =3	.56, df=1 (P=0.17), l ² =4	13.84%			
		Favours Fluoride 0.1	0.2 0.5 1 2 5	¹⁰ Favours Placebo	

Analysis 14.2. Comparison 14 Subgroup Osteoporosis definition, Outcome 2 No. People with new vertebral fractures - 4 years.

Study or subgroup	Favours Fluoride	Favours Placebo	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
14.2.1 Incident fractures					
Hansson 1987	0/25	1/25	4 •	0.59%	0.14[0,6.82]
Kleerekoper 1991	31/46	22/38		11.51%	1.5[0.62,3.63]
Pak 1995	7/54	22/56		12.64%	0.26[0.11,0.61]
Riggs 1990	40/101	45/101		29.04%	0.82[0.47,1.43]
Subtotal (95% CI)	226	220		53.78%	0.7[0.46,1.05]
Total events: 78 (Favours Fluoride), 90 ((Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =9.05, df=3	(P=0.03); I ² =66.84%				
Test for overall effect: Z=1.73(P=0.08)					
14.2.2 BMD					
Reginster 1998	1/100	7/100	↓	4.53%	0.21[0.05,0.87]
Subtotal (95% CI)	100	100		4.53%	0.21[0.05,0.87]
Total events: 1 (Favours Fluoride), 7 (Fa	avours Placebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=2.16(P=0.03)					
14.2.3 Fractures or BMD					
Pak 1995	7/54	22/56		12.64%	0.26[0.11,0.61]
Riggs 1990	40/101	45/101		29.04%	0.82[0.47,1.43]
Subtotal (95% CI)	155	157		41.68%	0.58[0.36,0.92]
Total events: 47 (Favours Fluoride), 67 ((Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =4.89, df=1	(P=0.03); I ² =79.55%				
Test for overall effect: Z=2.31(P=0.02)					
Total (95% CI)	481	477	•	100%	0.61[0.45,0.82]
Total events: 126 (Favours Fluoride), 16	64 (Favours Placebo)				
Heterogeneity: Tau ² =0; Chi ² =16.57, df=	6(P=0.01); I ² =63.78%				
Test for overall effect: Z=3.22(P=0)					
Test for subgroup differences: Chi ² =2.6	3, df=1 (P=0.27), I ² =23	8.99%			
	Fa	avours Fluoride	0.1 0.2 0.5 1 2 5	¹⁰ Favours Placebo	

Analysis 14.3. Comparison 14 Subgroup Osteoporosis definition, Outcome 3 Lumbar BMD % from baseline 2 years.

Study or subgroup	Favou	rs Fluoride	Favours Placebo		Mean Difference			Weight	Mean Difference	
	N	Mean(SD)	Ν	Mean(SD)		Fixed,	95% CI			Fixed, 95% CI
14.3.1 incident fractures										
Hansson 1987	24	114 (15.5)	22	101.8 (13.7)			-	\longrightarrow	0.87%	12.2[3.78,20.62]
Meunier 1998	147	110.8 (21.2)	113	102.4 (14.9)					3.19%	8.4[4.01,12.79]
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)				\rightarrow	5.1%	9.34[5.86,12.82]
Riggs 1990	100	121 (8.5)	101	100.5 (6.2)					14.58%	20.54[18.48,22.6]
Subtotal ***	319		287						23.74%	16.19[14.58,17.81]
Heterogeneity: Tau ² =0; Chi ² =45.04, df	=3(P<0.0	0001); I ² =93.34%								
Test for overall effect: Z=19.7(P<0.000	1)									
14.3.2 BMD					1					
			Fav	ours Fluoride	-10	-5	0	5 10	Favours Placeb	0

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Study or subgroup	Favou	ırs Fluoride	Favo	urs Placebo	Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed, 95% Cl		Fixed, 95% CI
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)	+	- 5.9%	6.2[2.97,9.43]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)		49.06%	8.04[6.92,9.16]
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)		1.61%	11.06[4.88,17.24]
Subtotal ***	147		154		•	56.58%	7.93[6.89,8.98]
Heterogeneity: Tau ² =0; Chi ² =2.12, d	f=2(P=0.3	5); I ² =5.79%					
Test for overall effect: Z=14.9(P<0.00	001)						
14.3.3 Fractures or BMD							
Pak 1995	48	109.6 (10.3)	51	100.3 (6.9)		5.1%	9.34[5.86,12.82]
Riggs 1990	100	121 (8.5)	101	100.5 (6.2)		14.58%	20.54[18.48,22.6]
Subtotal ***	148		152			19.68%	17.64[15.87,19.41]
Heterogeneity: Tau ² =0; Chi ² =29.53,	df=1(P<0.	0001); l ² =96.61%					
Test for overall effect: Z=19.53(P<0.0	0001)						
Total ***	614		593			100%	11.8[11.02,12.59]
Heterogeneity: Tau ² =0; Chi ² =199.68	, df=8(P<0	0.0001); I ² =95.999	%				
Test for overall effect: Z=29.46(P<0.0	0001)						
Test for subgroup differences: Chi ² =	122.99, d	f=1 (P<0.0001), I ²	=98.37%				
			Fav	ours Fluoride	-10 -5 0 5	¹⁰ Favours Pla	cebo

Analysis 14.4. Comparison 14 Subgroup Osteoporosis definition, Outcome 4 Lumbar BMD % from baseline 4 years.

Study or subgroup	Favou	rs Fluoride	Favou	ırs Placebo	Mean Di	fference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Fixed,	95% CI		Fixed, 95% CI
14.4.1 Incident fractures								
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)			3.4%	18.68[11.73,25.63]
Riggs 1990	100	139.6 (15)	101	102.7 (6.5)			16.07%	36.91[33.71,40.11]
Subtotal ***	148		152				19.47%	33.73[30.82,36.63]
Heterogeneity: Tau ² =0; Chi ² =21.8, df=	1(P<0.00	001); l ² =95.41%						
Test for overall effect: Z=22.76(P<0.00	01)							
14.4.2 BMD								
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)		-	61.07%	10.4[8.76.12.04]
Subtotal ***	100	(,	100				61.07%	10.4[8.76.12.04]
Heterogeneity: Not applicable								
Test for overall effect: Z=12.43(P<0.00	01)							
14.4.3 Fractures or BMD								
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)			3.4%	18.68[11.73,25.63]
Riggs 1990	100	139.6 (15)	101	102.7 (6.5)			16.07%	36.91[33.71,40.11]
Subtotal ***	148		152			,	19.47%	33.73[30.82,36.63]
Heterogeneity: Tau ² =0; Chi ² =21.8, df=	1(P<0.00	001); l ² =95.41%						
Test for overall effect: Z=22.76(P<0.00	01)							
Total ***	396		404				100%	19.48[18.2,20.76]
Heterogeneity: Tau ² =0; Chi ² =346.24, d	f=4(P<0	.0001); I ² =98.849	6					
Test for overall effect: Z=29.8(P<0.000	1)							
Test for subgroup differences: Chi ² =30)2.64, df	=1 (P<0.0001), I ²	=99.34%					
			Fav	ours Fluoride	-10 -5 0	0 5 10	Favours Place	bo

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Analysis 14.5. Comparison 14 Subgroup Osteoporosis definition, Outcome 5 GI minor overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
14.5.1 Incident fractures					
Grove 1981	1/14	1/14	+ + +	0.93%	1[0.06,16.85]
Hansson 1987	4/25	0/25		1.81%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38	•	7.85%	2.64[1,6.97]
Meunier 1998	123/208	87/146	— —	40.01%	0.98[0.64,1.51]
Pak 1995	5/54	4/56		4.02%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		4.26%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101	+	10.24%	2.56[1.09,6]
Subtotal (95% CI)	509	482	◆	69.12%	1.62[1.17,2.25]
Total events: 176 (Treatment), 105 (C	Control)				
Heterogeneity: Tau ² =0; Chi ² =22.23, d	lf=6(P=0); I ² =73.01%				
Test for overall effect: Z=2.91(P=0)					
14.5.2 BMD					
Gambacciani 1995	7/30	6/30		4.99%	1.21[0.36,4.1]
Sebert 1995	10/45	9/49		7.37%	1.27[0.46,3.45]
Subtotal (95% CI)	75	79		12.36%	1.24[0.57,2.7]
Total events: 17 (Treatment), 15 (Cor	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=0.96); I ² =0%				
Test for overall effect: Z=0.55(P=0.58))				
14.5.3 Fractures or BMD					
 Pak 1995	5/54	4/56		4 02%	1.32[0.34.5.14]
Riggs 1982	10/61	0/102		4 26%	16 93[4 53 63 26]
Riggs 1992	17/101	7/101		10.24%	2 56[1 09 6]
Subtotal (95% CI)	216	259		18.52%	3.43[1.82.6.45]
Total events: 32 (Treatment) 11 (Cor	atrol)	200		10.01/0	5110[2102,0110]
Heterogeneity: $Tau^2=0$: Chi ² =7 99 df	=2(P=0.02)·1 ² =74.95%				
Test for overall effect: 7=3 82(P=0)	-2(1-0.02),1-14.3370				
Total (95% CI)	800	820	•	100%	1.81[1.38,2.37]
Total events: 225 (Treatment), 131 (C	Control)				
Heterogeneity: Tau ² =0; Chi ² =35.46, d	lf=11(P=0); I ² =68.98%				
Test for overall effect: Z=4.25(P<0.00	01)				
Test for subgroup differences: Chi ² =5	5.24, df=1 (P=0.07), I ² =0	61.81%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 10	D Favours Control	

Analysis 14.6. Comparison 14 Subgroup Osteoporosis definition, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio						Weight	Peto Odds Ratio	
	n/N	n/N			Peto, Fi	ixed,	95% CI				Peto, Fixed, 95% Cl
14.6.1 Incident fractures											
Grove 1981	1/14	1/14	←			-			→	1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146			_		-			75.07%	0.98[0.64,1.51]
Subtotal (95% CI)	222	160			-	\blacklozenge	•			76.81%	0.98[0.64,1.5]
Total events: 124 (Treatment), 88 (Con	trol)										
	Fa	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.99); l ² =0%				
Test for overall effect: Z=0.08(P=0.93)					
14.6.2 BMD					
Gambacciani 1995	7/30	6/30		9.36%	1.21[0.36,4.1]
Sebert 1995	10/45	9/49	+	13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	75	79		23.19%	1.24[0.57,2.7]
Total events: 17 (Treatment), 15 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P	=0.96); l ² =0%				
Test for overall effect: Z=0.55(P=0.58)					
14.6.3 Fractures or BMD					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Contro	l)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	297	239	•	100%	1.04[0.71,1.51]
Total events: 141 (Treatment), 103 (Co	ontrol)				
Heterogeneity: Tau ² =0; Chi ² =0.28, df=3	8(P=0.96); I ² =0%				
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi ² =0.2	28, df=1 (P=0.6), I ² =0	%			
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 14.7. Comparison 14 Subgroup Osteoporosis definition, Outcome 7 GI minor 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% CI
14.7.1 Incident fractures					
Kleerekoper 1991	16/46	6/38	•	- 17.48%	2.64[1,6.97]
Pak 1995	5/54	4/56	+	8.95%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		9.5%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		22.81%	2.56[1.09,6]
Subtotal (95% CI)	262	297		58.74%	3.17[1.87,5.39]
Total events: 48 (Treatment), 17 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =8.18, df=3	8(P=0.04); I ² =63.33%				
Test for overall effect: Z=4.27(P<0.0001	L)				
14.7.2 BMD					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
14.7.3 Fractures or BMD					
Pak 1995	5/54	4/56	+	8.95%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		9.5%	16.93[4.53,63.26]
Riggs 1990	17/101	7/101		22.81%	2.56[1.09,6]
Subtotal (95% CI)	216	259		41.26%	3.43[1.82,6.45]
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

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Study or subgroup	Treatment	Control			Peto	Odds	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed,	95% CI				Peto, Fixed, 95% Cl
Total events: 32 (Treatment), 11 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =7.99, d	f=2(P=0.02); I ² =74.95%										
Test for overall effect: Z=3.82(P=0)											
Total (95% CI)	478	556								100%	3.28[2.18,4.92]
Total events: 80 (Treatment), 28 (Co	ntrol)										
Heterogeneity: Tau ² =0; Chi ² =16.2, d	f=6(P=0.01); I ² =62.96%										
Test for overall effect: Z=5.73(P<0.00	001)										
Test for subgroup differences: Chi ² =	0.03, df=1 (P=0.85), I ² =0%	1									
	Favo	urs Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

Analysis 14.8. Comparison 14 Subgroup Osteoporosis definition, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
14.8.1 Incident fractures					
Kleerekoper 1991	13/46	7/38		8.1%	1.71[0.63,4.66]
Meunier 1998	29/208	17/146		20.63%	1.22[0.65,2.3]
Pak 1995	3/54	5/56		3.97%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101	- _	26.24%	4.46[2.56,7.79]
Subtotal (95% CI)	409	341	•	58.94%	2.18[1.5,3.15]
Total events: 106 (Treatment), 53 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =12.85, df=	3(P=0); I ² =76.65%				
Test for overall effect: Z=4.1(P<0.0001)					
14.8.2 BMD					
Reginster 1998	12/100	11/100	+	10.85%	1.1[0.46,2.62]
Subtotal (95% CI)	100	100		10.85%	1.1[0.46,2.62]
Total events: 12 (Treatment), 11 (Contr	rol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.83)					
14.8.3 Fractures or BMD					
Pak 1995	3/54	5/56		3.97%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101		26.24%	4.46[2.56,7.79]
Subtotal (95% CI)	155	157		30.21%	3.43[2.04,5.77]
Total events: 64 (Treatment), 29 (Contr	rol)				
Heterogeneity: Tau ² =0; Chi ² =6.44, df=1	(P=0.01); I ² =84.48%				
Test for overall effect: Z=4.66(P<0.0001)				
Total (95% CI)	664	598	•	100%	2.32[1.74,3.09]
Total events: 182 (Treatment), 93 (Con	trol)				
Heterogeneity: Tau ² =0; Chi ² =24.43, df=	6(P=0); I ² =75.44%				
Test for overall effect: Z=5.78(P<0.0001)				
Test for subgroup differences: Chi ² =5.1	4, df=1 (P=0.08), I ² =0	51.08%			
	Fa	vours Treatment 0.2	1 0.2 0.5 1 2 5 10	⁾ Favours Control	

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Study or subgroup	Treatment	Control	Peto Od	lds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixe	ed, 95% CI		Peto, Fixed, 95% Cl
14.9.1 Incident fractures						
Meunier 1998	29/208	17/146			100%	1.22[0.65,2.3]
Subtotal (95% CI)	208	146			100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
14.9.2 BMD						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control)						
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
14.9.3 Fractures or BMD						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Control)						
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)	208	146			100%	1.22[0.65,2.3]
Total events: 29 (Treatment), 17 (Contro	l)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
Test for subgroup differences: Not applie	cable					
	F	avours Treatment	0.1 0.2 0.5	1 2 5	¹⁰ Favours Control	

Analysis 14.9. Comparison 14 Subgroup Osteoporosis definition, Outcome 9 Non vertebral fractures 2 years.

Analysis 14.10. Comparison 14 Subgroup Osteoporosis definition, Outcome 10 Non vertebral fractures 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
14.10.1 Incident fractures					
Kleerekoper 1991	13/46	7/38		10.21%	1.71[0.63,4.66]
Pak 1995	3/54	5/56	+	5%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101	_ 	33.06%	4.46[2.56,7.79]
Subtotal (95% CI)	201	195	•	48.27%	2.96[1.87,4.7]
Total events: 77 (Treatment), 36 (Cont	trol)				
Heterogeneity: Tau ² =0; Chi ² =7.91, df=	2(P=0.02); I ² =74.72%				
Test for overall effect: Z=4.62(P<0.000	1)				
14.10.2 BMD					
Reginster 1998	12/100	11/100		13.67%	1.1[0.46,2.62]
Subtotal (95% CI)	100	100		13.67%	1.1[0.46,2.62]
Total events: 12 (Treatment), 11 (Cont	trol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.83)					
14.10.3 Fractures or BMD					
Pak 1995	3/54	5/56	• • •	5%	0.61[0.15,2.55]
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5 1	⁰ Favours Control	

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Study or subgroup	Treatment	Control	Peto Oc	Peto Odds Ratio		Peto Odds Ratio
	n/N	n/N	Peto, Fix	Peto, Fixed, 95% Cl		Peto, Fixed, 95% Cl
Riggs 1990	61/101	24/101			33.06%	4.46[2.56,7.79]
Subtotal (95% CI)	155	157			38.06%	3.43[2.04,5.77]
Total events: 64 (Treatment), 29 (Co	ntrol)					
Heterogeneity: Tau ² =0; Chi ² =6.44, df	=1(P=0.01); I ² =84.48%					
Test for overall effect: Z=4.66(P<0.00	01)					
Total (95% CI)	456	452		•	100%	2.74[1.99.3.77]
Total events: 153 (Treatment), 76 (Co	ontrol)					
Heterogeneity: Tau ² =0; Chi ² =19.43, c	lf=5(P=0); I ² =74.27%					
Test for overall effect: Z=6.16(P<0.00	01)					
Test for subgroup differences: Chi ² =	5.08, df=1 (P=0.08), I ² =6	60.6%				
	Fai	vours Trootmont	01 02 05	1 2 5 10	Fougurs Control	

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 14.11. Comparison 14 Subgroup Osteoporosis definition, Outcome 11 Lower limb pain syndrome.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
14.11.1 BMD					
Kleerekoper 1991	23/46	13/38	+	11.44%	1.89[0.8,4.48]
Meunier 1998	37/208	7/146		20.78%	3.29[1.73,6.24]
Pak 1995	6/54	8/56	+	6.84%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		6.69%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101	+	18.55%	6.78[3.44,13.36]
Subtotal (95% CI)	470	443	•	64.3%	3.75[2.61,5.4]
Total events: 117 (Treatment), 33 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =21.01, df=	=4(P=0); I ² =80.96%				
Test for overall effect: Z=7.12(P<0.000)	L)				
14.11.2 BMD					
Sebert 1995	5/45	2/49		3.63%	2.74[0.59,12.71]
Subtotal (95% CI)	45	49		3.63%	2.74[0.59,12.71]
Total events: 5 (Treatment), 2 (Control	l)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					
14.11.3 Fractures or BMD					
Pak 1995	6/54	8/56	+	6.84%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		6.69%	18.27[5.91,56.48]
Riggs 1990	37/101	5/101	+	18.55%	6.78[3.44,13.36]
Subtotal (95% CI)	216	259		32.08%	5.22[3.12,8.74]
Total events: 57 (Treatment), 13 (Cont	rol)				
Heterogeneity: Tau ² =0; Chi ² =16.85, df=	=2(P=0); I ² =88.13%				
Test for overall effect: Z=6.28(P<0.000)	L)				
Total (95% CI)	731	751	•	100%	4.12[3.08,5.52]
Total events: 179 (Treatment), 48 (Con	itrol)				
Heterogeneity: Tau ² =0; Chi ² =39.2, df=8	8(P<0.0001); I ² =79.59	%			
Test for overall effect: Z=9.51(P<0.000)	L)				
Test for subgroup differences: Chi ² =1.3	33, df=1 (P=0.51), I ² =0	0%			
	Fa	vours Treatment 0.1	0.2 0.5 1 2 5 10	Favours Control	

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Analysis 14.12. Comparison 14 Subgroup Osteoporosis definition, Outcome 12 Withdrawals and dropouts overall.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% Cl
14.12.1 Incident fractures					
Grove 1981	2/14	4/14		2.34%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25		1.79%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	29/38		8%	0.72[0.27,1.86]
Pak 1995	6/54	5/56		4.77%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101		21.5%	1.14[0.64,2.05]
Subtotal (95% CI)	240	234	•	38.41%	0.94[0.61,1.45]
Total events: 76 (Treatment), 7	'3 (Control)				
Heterogeneity: Tau ² =0; Chi ² =2.	61, df=4(P=0.62); I ² =0%				
Test for overall effect: Z=0.29(P	P=0.77)				
14.12.2 BMD					
Gambacciani 1995	9/30	9/30		6.12%	1[0.33,2.99]
Reginster 1998	38/100	40/100		22.85%	0.92[0.52,1.62]
Sebert 1995	9/35	8/41	+	6.35%	1.42[0.49,4.17]
Subtotal (95% CI)	165	171	-	35.32%	1.01[0.64,1.59]
Total events: 56 (Treatment), 5	7 (Control)				
Heterogeneity: Tau ² =0; Chi ² =0.	49, df=2(P=0.78); I ² =0%				
Test for overall effect: Z=0.04(P	P=0.97)				
14.12.3 Fractures or BMD					
Pak 1995	6/54	5/56		4.77%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101		21.5%	1.14[0.64,2.05]
Subtotal (95% CI)	155	157		26.27%	1.17[0.69,1.98]
Total events: 41 (Treatment), 3	37 (Control)				
Heterogeneity: Tau ² =0; Chi ² =0.	02, df=1(P=0.88); I ² =0%				
Test for overall effect: Z=0.57(P	P=0.57)				
Total (95% CI)	560	562	•	100%	1.02[0.78,1.34]
Total events: 173 (Treatment),	167 (Control)				
Heterogeneity: Tau ² =0; Chi ² =3.	52, df=9(P=0.94); I ² =0%				
Test for overall effect: Z=0.13(P	P=0.89)				
Test for subgroup differences:	Chi ² =0.39, df=1 (P=0.82), I ² =	0%			
	Fa	vours Treatment 0.1	0.2 0.5 1 2 5	¹⁰ Favours Control	

Analysis 14.13. Comparison 14 Subgroup Osteoporosis definition, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio			Weight	Peto Odds Ratio				
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% Cl
14.13.1 Incident fractures											
Grove 1981	2/14	4/14	←		•	_				15.77%	0.44[0.07,2.6]
Subtotal (95% CI)	14	14								15.77%	0.44[0.07,2.6]
Total events: 2 (Treatment), 4 (Contro	!)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.9(P=0.37)											
	Fav	vours Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

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Study or subgroup	Treatment	Control	Peto Odds R	atio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 9	5% CI		Peto, Fixed, 95% CI
14.13.2 BMD						
Gambacciani 1995	9/30	9/30			41.34%	1[0.33,2.99]
Sebert 1995	9/35	8/41			42.88%	1.42[0.49,4.17]
Subtotal (95% CI)	65	71			84.23%	1.2[0.56,2.58]
Total events: 18 (Treatment), 17 (0	Control)					
Heterogeneity: Tau ² =0; Chi ² =0.2, c	lf=1(P=0.65); l ² =0%					
Test for overall effect: Z=0.46(P=0.	65)					
14.13.3 Fractures or BMD						
Subtotal (95% CI)	0	0				Not estimable
Total events: 0 (Treatment), 0 (Co	ntrol)					
Heterogeneity: Not applicable						
Test for overall effect: Not applica	ble					
Total (95% CI)	79	85	-		100%	1.02[0.51,2.07]
Total events: 20 (Treatment), 21 (0	Control)					
Heterogeneity: Tau ² =0; Chi ² =1.23,	df=2(P=0.54); I ² =0%					
Test for overall effect: Z=0.06(P=0.95)						
Test for subgroup differences: Chi ² =1.02, df=1 (P=0.31), l ² =2.4%						
	Fa	vours Treatment	0.1 0.2 0.5 1	2 5 10	Favours Control	

Analysis 14.14. Comparison 14 Subgroup Osteoporosis definition, Outcome 14 Withdrawals and dropouts 4 years.

Study or subgroup	Treatment	Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
14.14.1 Incident fractures					
Hansson 1987	1/25	3/25	+	2.32%	0.34[0.05,2.61]
Pak 1995	6/54	5/56	+	6.18%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101		27.86%	1.14[0.64,2.05]
Subtotal (95% CI)	180	182	-	36.36%	1.08[0.65,1.8]
Total events: 42 (Treatment), 40 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =1.33, d	f=2(P=0.52); I ² =0%				
Test for overall effect: Z=0.29(P=0.77	7)				
14.14.2 BMD					
Reginster 1998	38/100	40/100		29.6%	0.92[0.52,1.62]
Subtotal (95% CI)	100	100		29.6%	0.92[0.52,1.62]
Total events: 38 (Treatment), 40 (Co	ntrol)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77	7)				
14.14.3 Fractures or BMD					
Pak 1995	6/54	5/56		6.18%	1.27[0.37,4.4]
Riggs 1990	35/101	32/101		27.86%	1.14[0.64,2.05]
Subtotal (95% CI)	155	157		34.04%	1.17[0.69,1.98]
Total events: 41 (Treatment), 37 (Co	ntrol)				
Heterogeneity: Tau ² =0; Chi ² =0.02, d	f=1(P=0.88); I ² =0%				
Test for overall effect: Z=0.57(P=0.57	7)				
	Fa	vours Treatment	0.1 0.2 0.5 1 2 5	¹⁰ Favours Control	

Fluoride for treating postmenopausal osteoporosis (Review)



Study or subgroup	Treatment	Control			Peto	Odds F	Ratio			Weight	Peto Odds Ratio
	n/N	n/N			Peto, F	ixed, 9	95% CI				Peto, Fixed, 95% CI
Total (95% CI)	435	439				+				100%	1.06[0.78,1.44]
Total events: 121 (Treatment), 117 (Control)											
Heterogeneity: Tau ² =0; Chi ² =1.72, df=5(P=0.89); I ² =0%											
Test for overall effect: Z=0.35(P=0.73	3)										
Test for subgroup differences: Chi ² =	-0.37, df=1 (P=0.83), I ² =09	6									
	Favo	urs Treatment	0.1	0.2	0.5	1	2	5	10	Favours Control	

WHAT'S NEW

Date	Event	Description
17 September 2008	Amended	Converted to new review format. C038-R

CONTRIBUTIONS OF AUTHORS

DH was responsible for the development of the protocol and the overall content for the review.

VW was involved in the selection of the articles, data abstraction, drafting in the final review.

BS was involved in the quality assessment, provided methodological advice and contributed to the development of the review and the final version.

PT was responsible for the content development throughout the protocol and review stage.

GW provided statistical support throughout the review process, and had extensive input into the analytic section of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Ottawa, Canada.
- Loeb Health Research Institute, Canada.

External sources

• No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density [drug effects]; Fluorides [*therapeutic use]; Fractures, Bone [prevention & control]; Osteoporosis, Postmenopausal [*drug therapy]; Phosphates [*therapeutic use]; Randomized Controlled Trials as Topic; Sodium Fluoride [*therapeutic use]

MeSH check words

Female; Humans