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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 micro-architectural 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

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

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 non-vertebral 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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CHARACTERISTICS OF STUDIES

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

Christiansen 1980

Methods	RCT duration 24 months10 groups for randomisation. 56 patients in 2 fluoride groups and 259 in 8 control groups
Participants	315 post menopausal women Denmark age 50.1 time since menopause 19.1 months race NA
Interventions	Na F 9 mg element (low dose), non enteric coated, non slow-releaseassociated treatment calciumversus HRT Thiazides, vit D or 1 alpha vit D
Outcomes	%change in BMC forearm
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

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 fluoride (low dose), non enteric-coated, non slow-release associated treatment calciumversus placebo
Outcomes	BMD lumbar, total body, legs, arms GI side effects
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 women with backpain and vertebral fracture age 73.9 menopause duration NA race NA
Interventions	NaF 9 mg fluoride element (low dose), non enteric-coated, non slow-release associated treatment calcium plus vitamine Dversus placebo
Outcomes	forearm cnange in BMC, pain sore, strenght score, metacarpal index
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

Hansson 1987

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

Hansson 1987 *(Continued)*

	age 66 duration of menopause NA race 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 dropouts 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

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 vertebral fractures, lumbar and femoral neck BMD, lower limb pain syndrome and GI side effects
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

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

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 in 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 except hip ; mean age 63.5 ; mean age at menopause 48.5
Interventions	MPF 20 mg Fluoride element (low dose), non enteric-coated, non slow-release associated treatment calcium 1000mgversus placebo
Outcomes	Fractures : - vertebral and non vertebral BMD : - lumbar and total hip
Notes	Quality score 5 randomization 2 blinding 2 withdrawals and dropouts 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

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 element (high dose), non enteric-coated, non slow-releaseversus placebo associated treatment calcium
Outcomes	lumbar BMD, vertebral and non vertebral fractures, BMD femoral neck and femoral trochanter , GI side effects
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

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

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

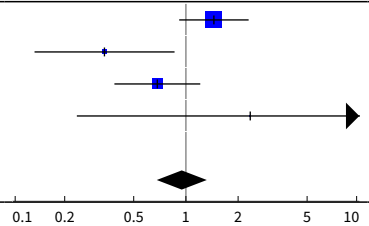
Comparison 1. Fluoride vs Placebo - Overall

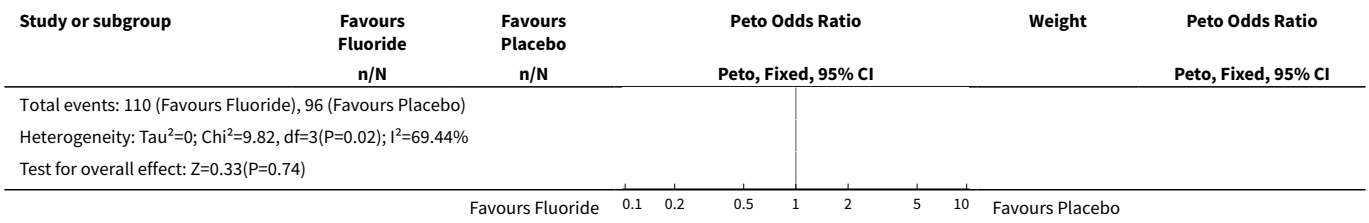
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures - 2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	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 baseline 2 years	3	650	Mean Difference (IV, Fixed, 95% CI)	2.65 [1.93, 3.38]
11 Best available hip % from baseline 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]

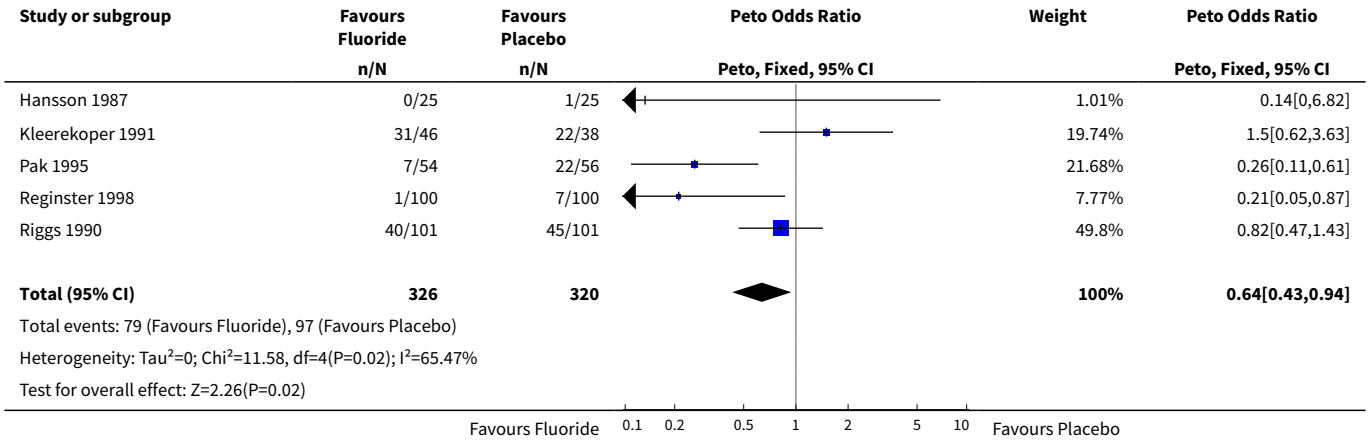
Analysis 1.1. Comparison 1 Fluoride vs Placebo - Overall, Outcome 1 No. People with new vertebral fractures - 2 years.

Study or subgroup	Favours Fluoride n/N	Favours Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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]**

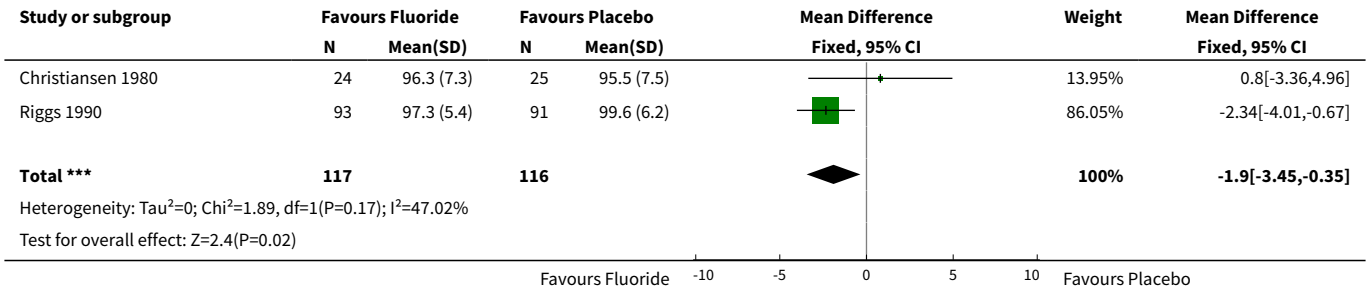




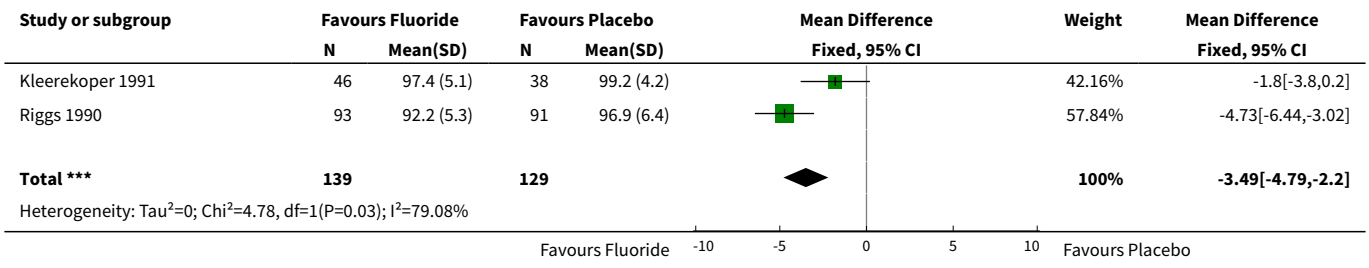
Analysis 1.2. Comparison 1 Fluoride vs Placebo - Overall, Outcome 2 No. People with new vertebral fractures - 4 years.



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



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



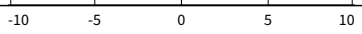
Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=5.28(P<0.0001)							

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

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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)							

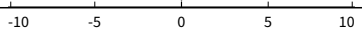
Analysis 1.6. Comparison 1 Fluoride vs Placebo - Overall, Outcome 6 Legs BMD % from baseline.

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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)							



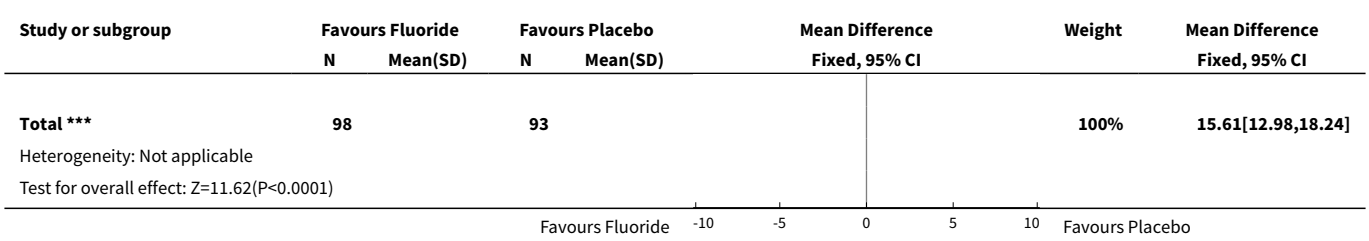
Analysis 1.7. Comparison 1 Fluoride vs Placebo - Overall, Outcome 7 Arms BMD % from baseline.

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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)							

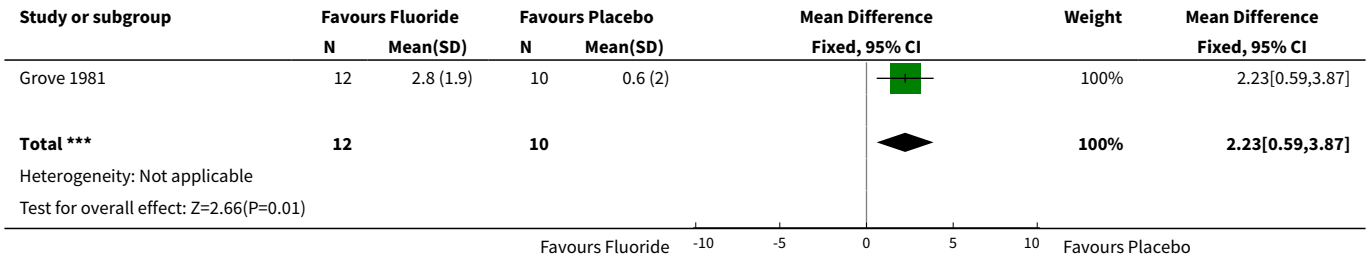


Analysis 1.8. Comparison 1 Fluoride vs Placebo - Overall, Outcome 8 Femoral trochanter BMD % from baseline 4 years.

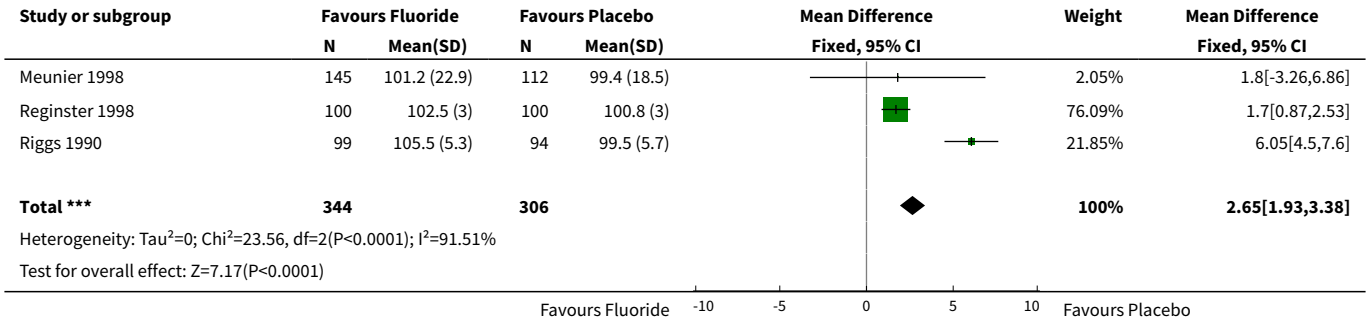
Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Riggs 1990	98	116.2 (11.1)	93	100.6 (7.2)		100%	15.61[12.98,18.24]



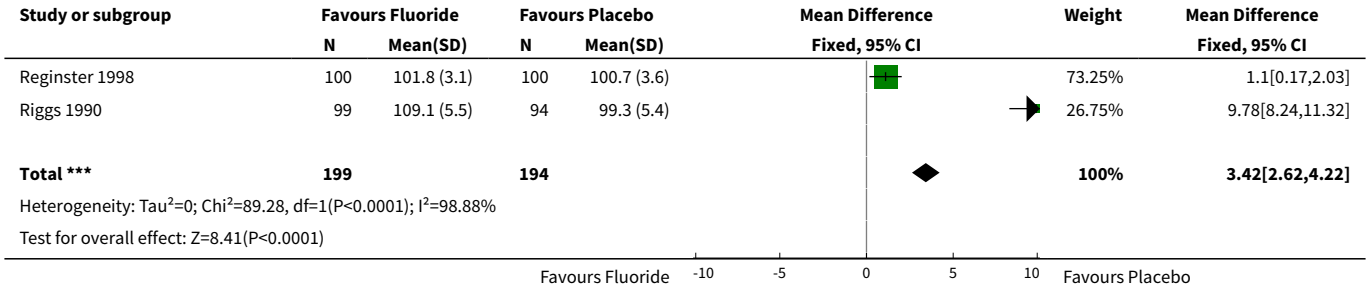
Analysis 1.9. Comparison 1 Fluoride vs Placebo - Overall, Outcome 9 Pain mobility score- change from baseline.



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



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

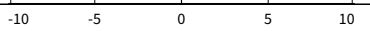


Analysis 1.12. Comparison 1 Fluoride vs Placebo - Overall, Outcome 12 Height % from baseline 4 years.

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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); I^2=64.97%							
Test for overall effect: Z=1.53(P=0.13)							

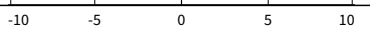
Analysis 1.13. Comparison 1 Fluoride vs Placebo - Overall, Outcome 13 Lumbar BMD % from baseline 2 years.

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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<0.0001); I^2=94.93%							
Test for overall effect: Z=23.21(P<0.0001)							



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

Study or subgroup	Favours Fluoride N	Mean(SD)	Favours Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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, df=2(P<0.0001); I^2=99.05%							
Test for overall effect: Z=22.01(P<0.0001)							



Comparison 2. Side effects

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

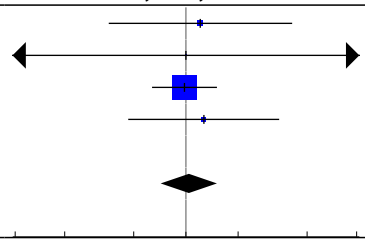
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 GI minor overall 2 years	4	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.71, 1.51]
3 GI minor overall 4 years	4	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [1.87, 5.39]
4 GI Minor Nausea	1	28	Peto Odds 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]

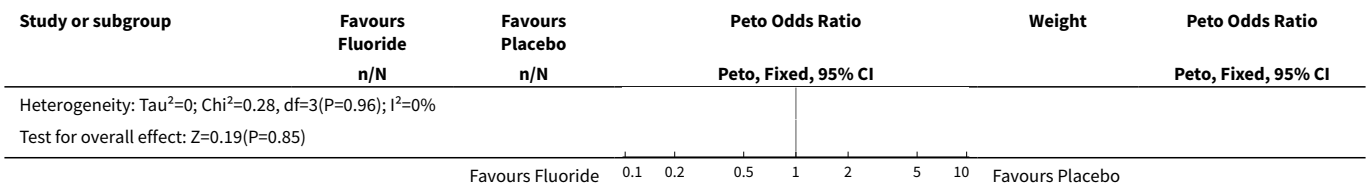
Analysis 2.1. Comparison 2 Side effects, Outcome 1 GI Minor Overall.

Study or subgroup	Favours Fluoride n/N	Favours Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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]
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), 120 (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)					

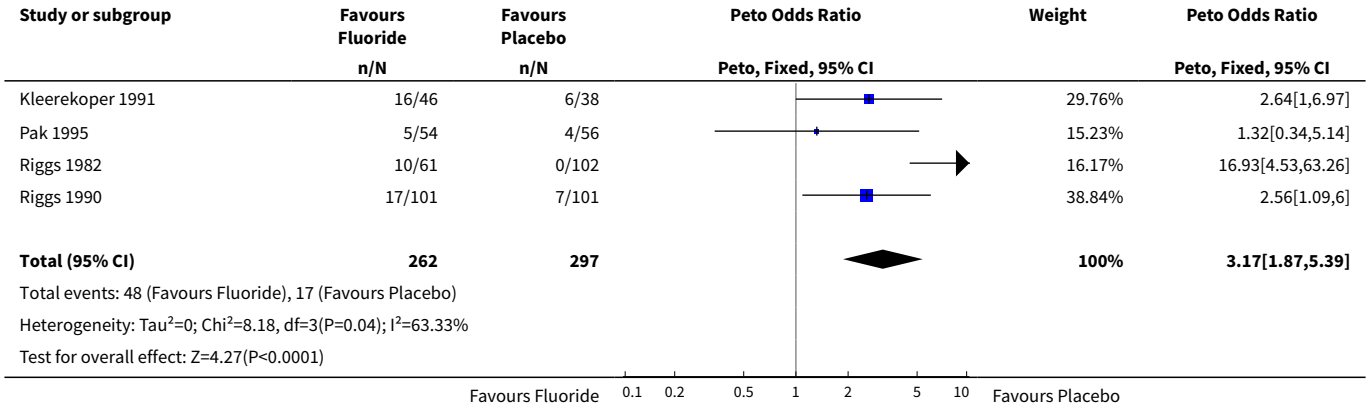
Analysis 2.2. Comparison 2 Side effects, Outcome 2 GI minor overall 2 years.

Study or subgroup	Favours Fluoride n/N	Favours Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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), 103 (Favours Placebo)					

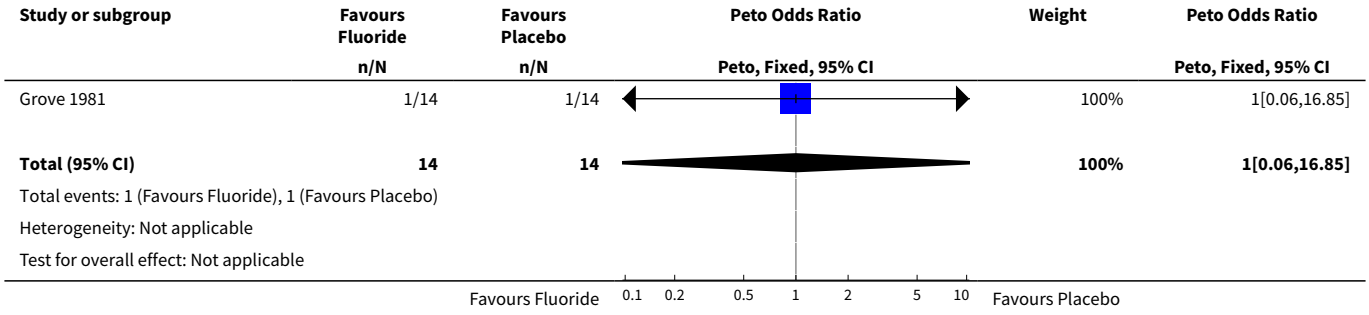




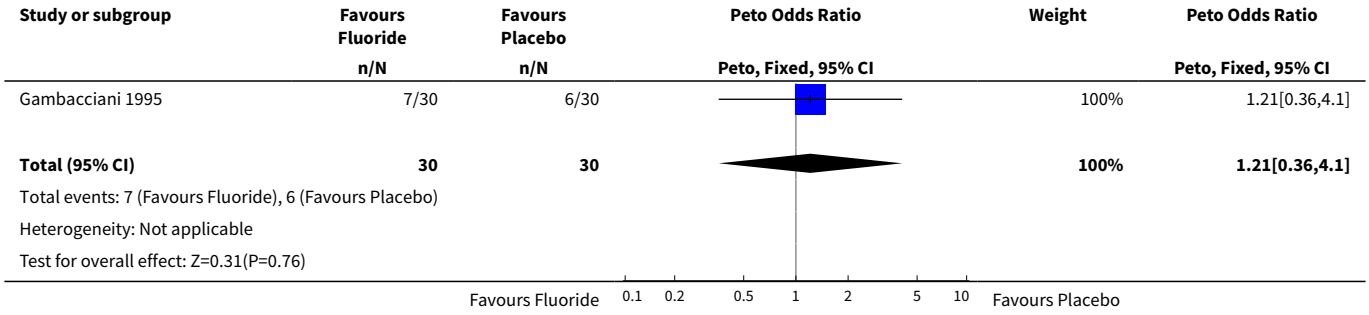
Analysis 2.3. Comparison 2 Side effects, Outcome 3 GI minor overall 4 years.



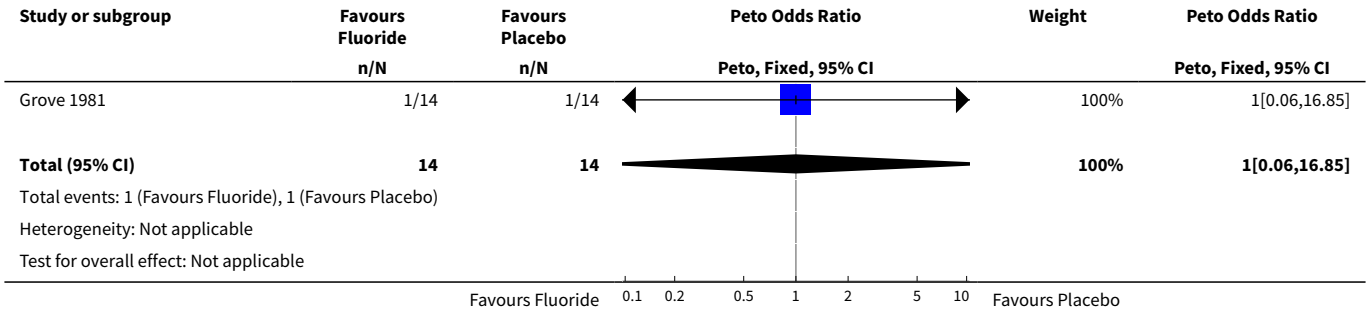
Analysis 2.4. Comparison 2 Side effects, Outcome 4 GI Minor Nausea.



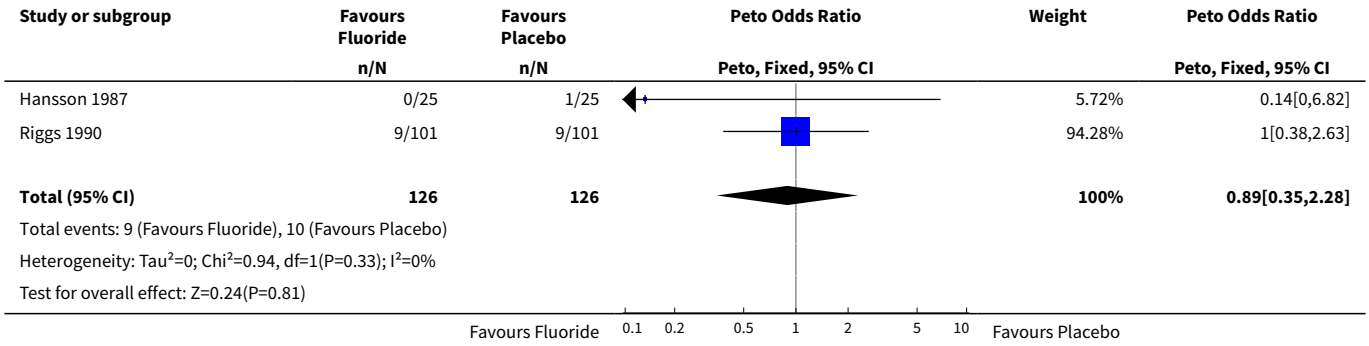
Analysis 2.5. Comparison 2 Side effects, Outcome 5 GI Minor pain.



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



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



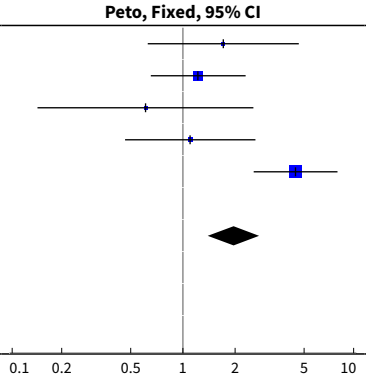
Comparison 3. Number of patients with new nonvertebral fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nonvertebral fractures 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]

Outcome or subgroup title	No. of studies	No. of participants	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 microfractures	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 fracture overall 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]
14 Non vertebral fracture 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]

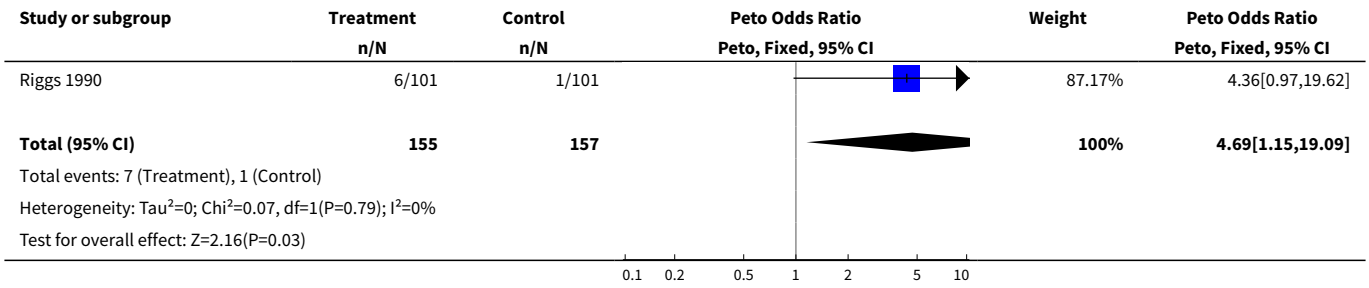
Analysis 3.1. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 1 Nonvertebral fractures overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (Control)					
Heterogeneity: Tau²=0; Chi²=14.84, df=4(P=0.01); I²=73.05%					
Test for overall effect: Z=3.85(P=0)					

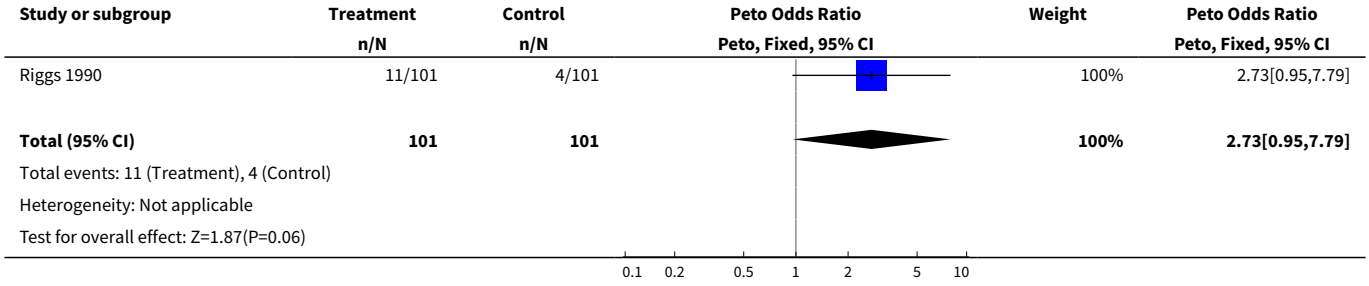


Analysis 3.2. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 2 Pelvis 4 years.

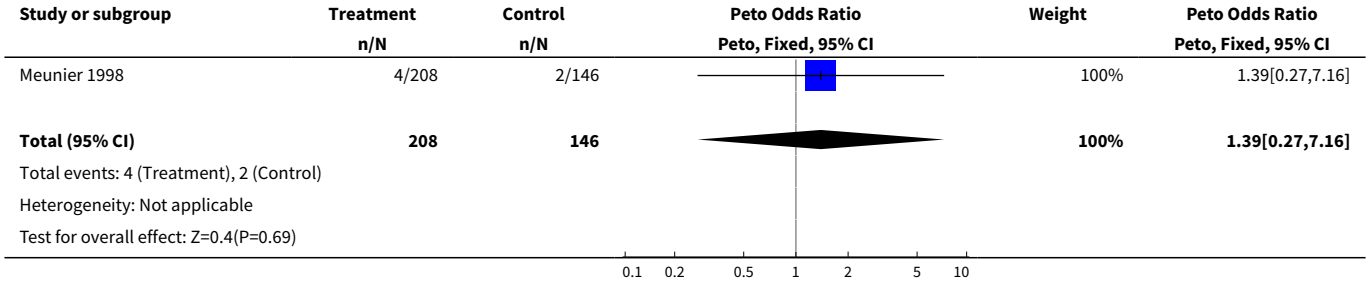
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pak 1995	1/54	0/56		12.83%	7.67[0.15,386.69]



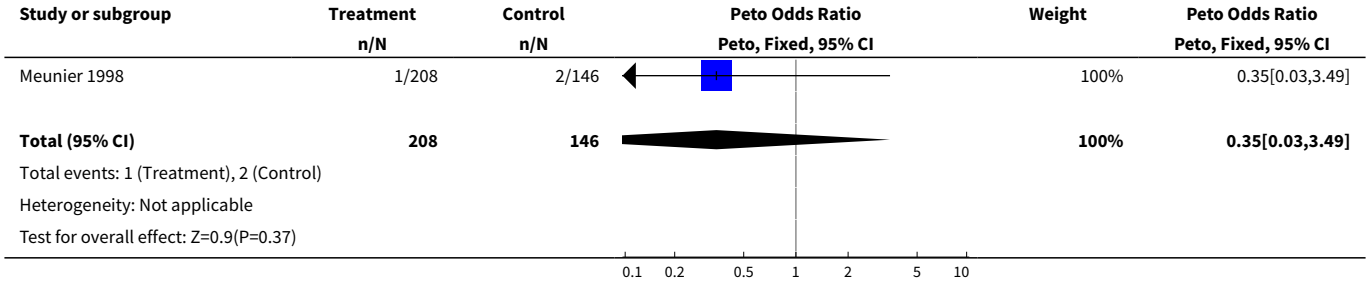
Analysis 3.3. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 3 Proximal Femur 4 years.



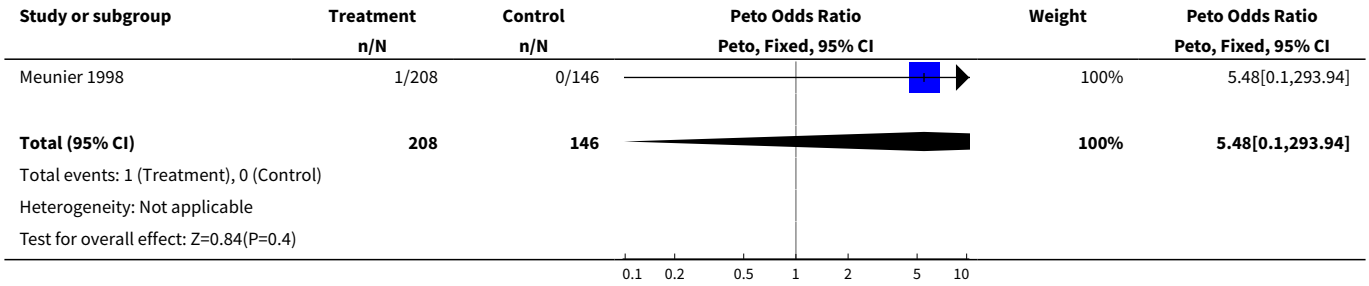
Analysis 3.4. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 4 Hip 2 years.



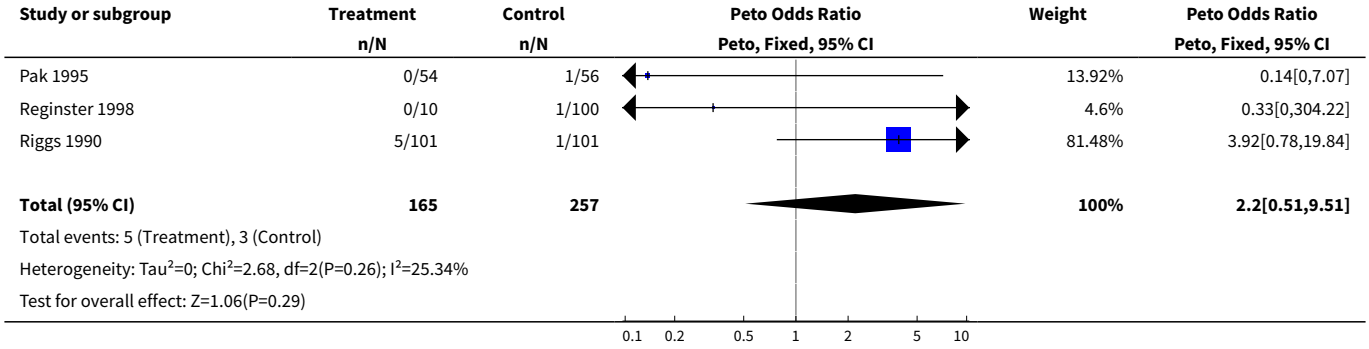
Analysis 3.5. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 5 Foot 2 years.



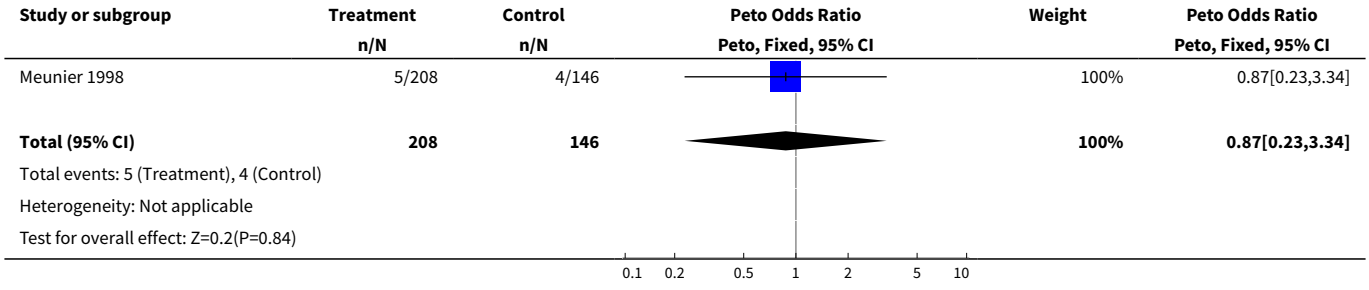
Analysis 3.6. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 6 Tibia 2 years.



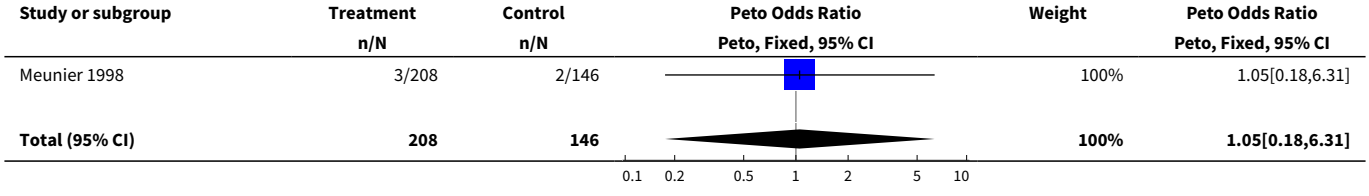
Analysis 3.7. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 7 Humerus 4 years.

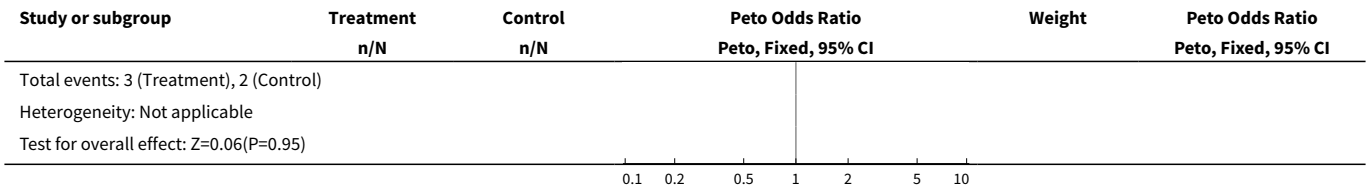


Analysis 3.8. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 8 Wrist 2 years.

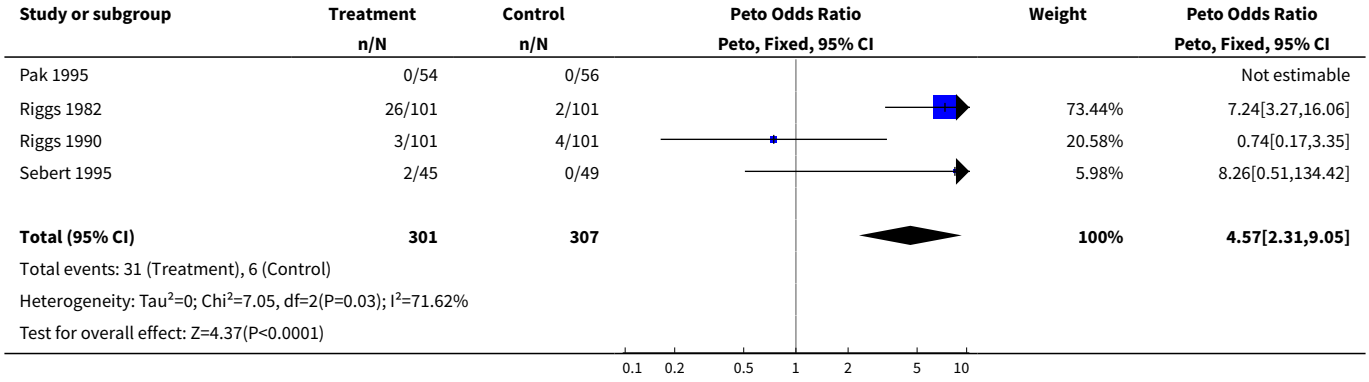


Analysis 3.9. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 9 Rib 2 years.

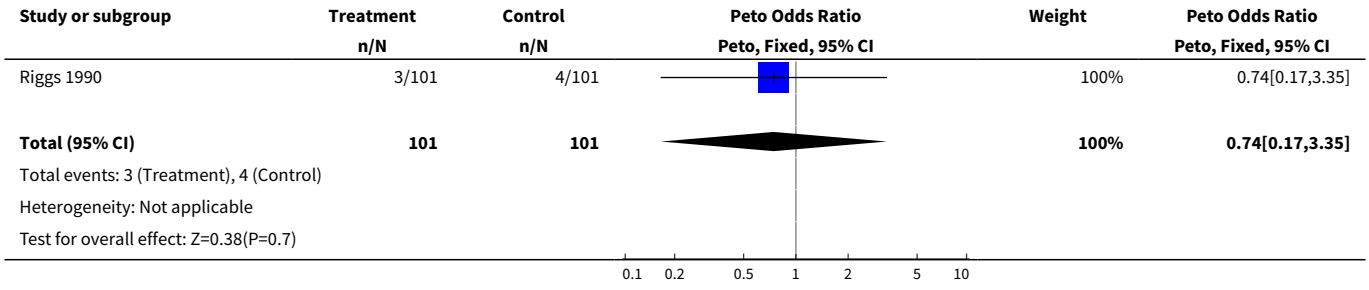




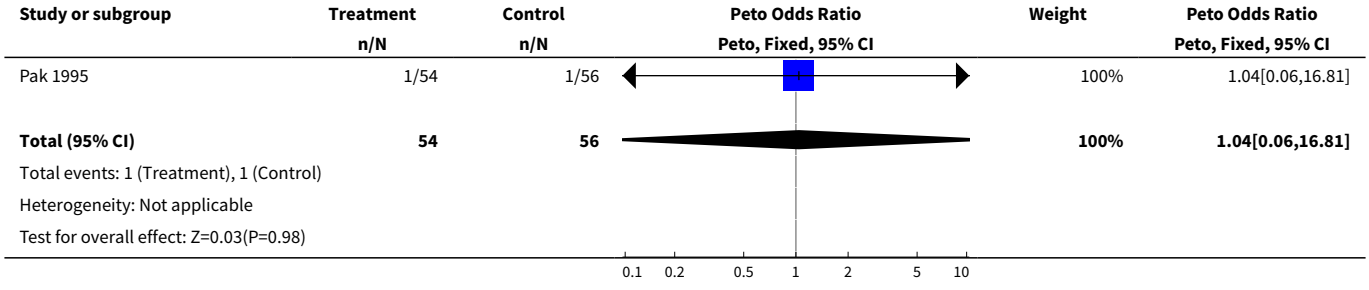
Analysis 3.10. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 10 Fissures or microfractures.



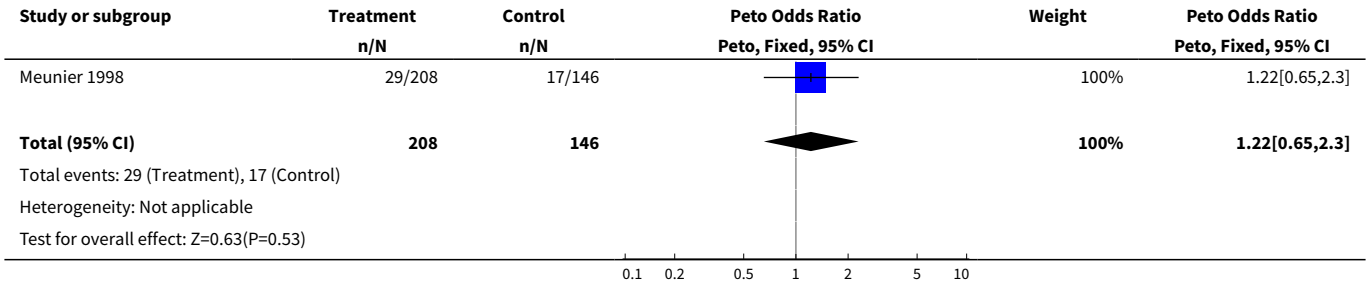
Analysis 3.11. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 11 Bone spurs.



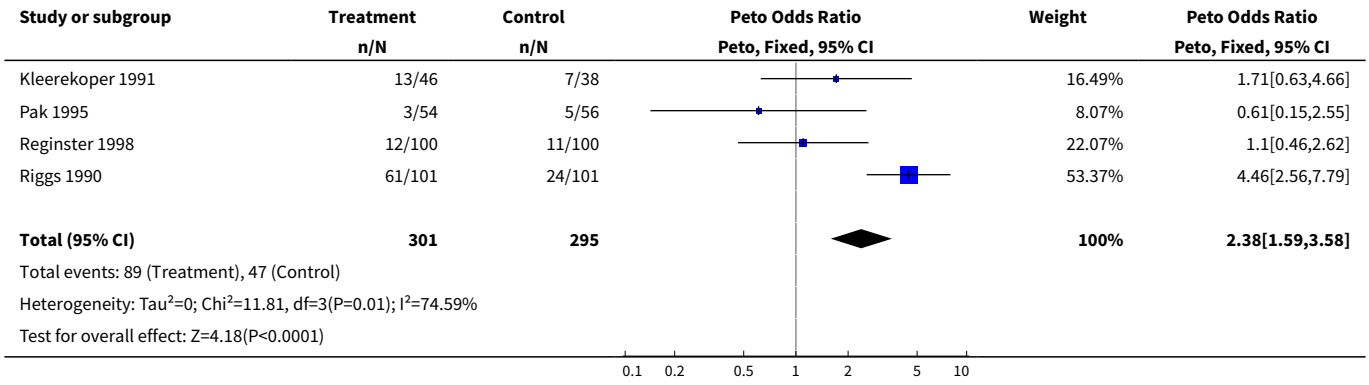
Analysis 3.12. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 12 Traumatic fractures.



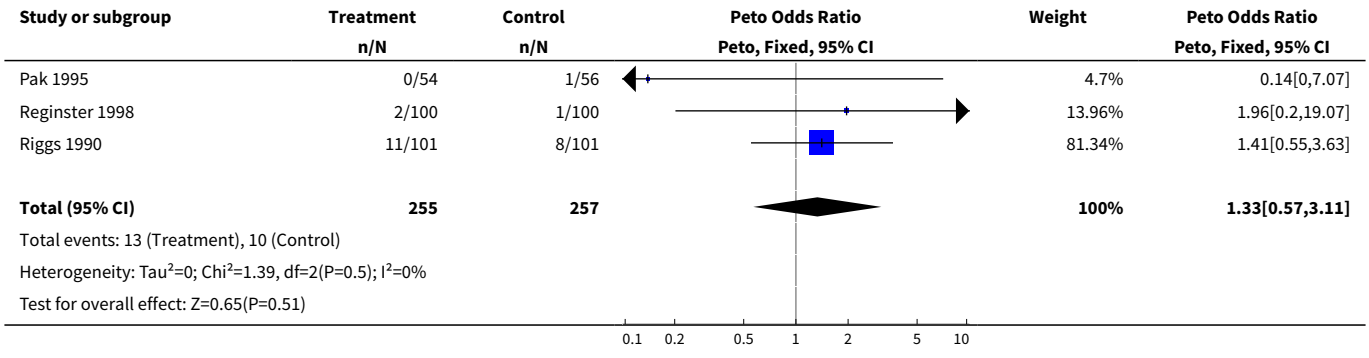
Analysis 3.13. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 13 Non vertebral fracture overall 2 years.



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

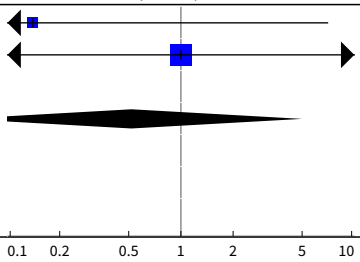


Analysis 3.15. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 15 Rib 4 years.



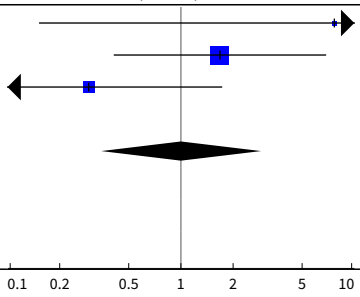
Analysis 3.16. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 16 Hip 4 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (Control)					
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)					



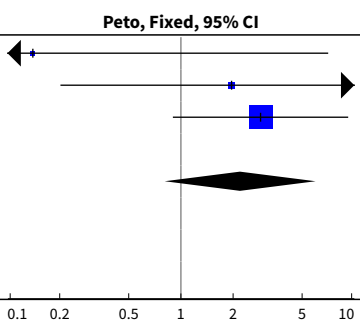
Analysis 3.17. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 17 Wrist 4 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.39, df=2(P=0.18); I^2=41.03%					
Test for overall effect: Z=0(P=1)					



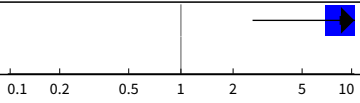
Analysis 3.18. Comparison 3 Number of patients with new nonvertebral fractures, Outcome 18 Foot 4 years.

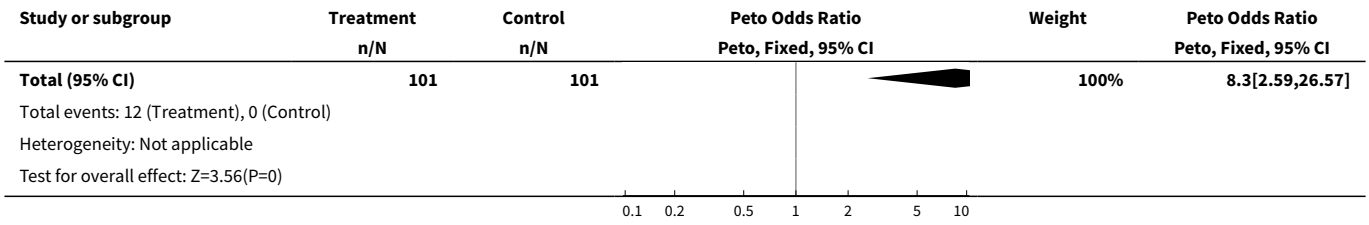
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pak 1995	0/54	1/56		6.53%	0.14[0,7.07]
Reginster 1998	2/100	1/100		19.39%	1.96[0.2,19.07]
Riggs 1990	9/101	3/101		74.08%	2.88[0.9,9.22]
Total (95% CI)	**255**	**257**		**100%**	**2.19[0.81,5.98]**
Total events: 11 (Treatment), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.11, df=2(P=0.35); I^2=5.19%					
Test for overall effect: Z=1.54(P=0.12)					



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

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Riggs 1990	12/101	0/101		100%	8.3[2.59,26.57]

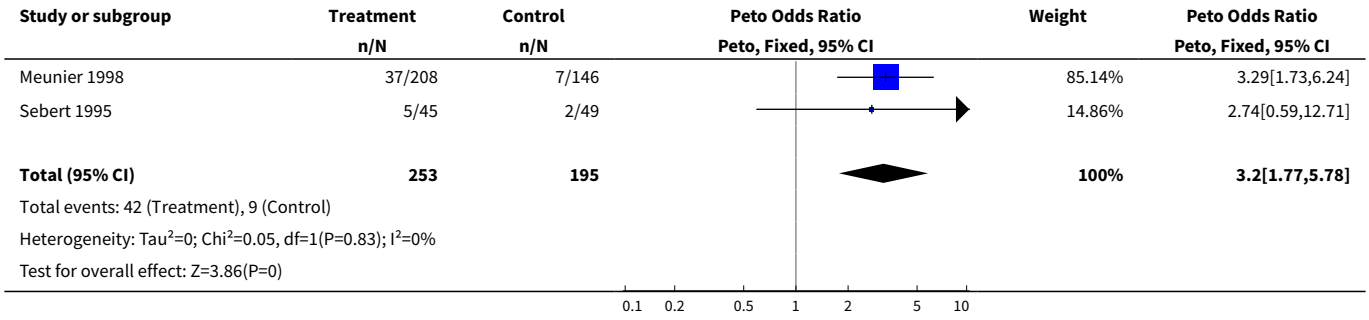




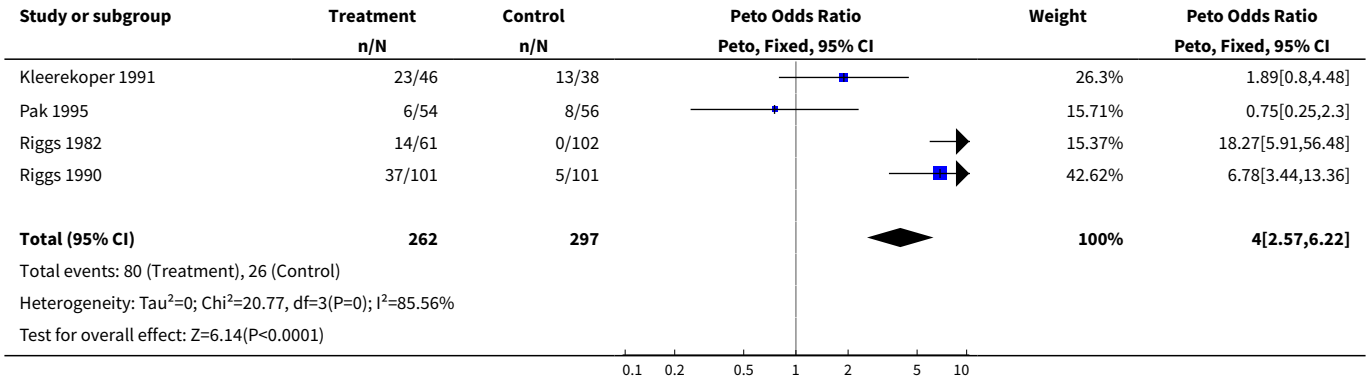
Comparison 4. Musculoskeletal pain

Outcome or subgroup title	No. of studies	No. of participants	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]

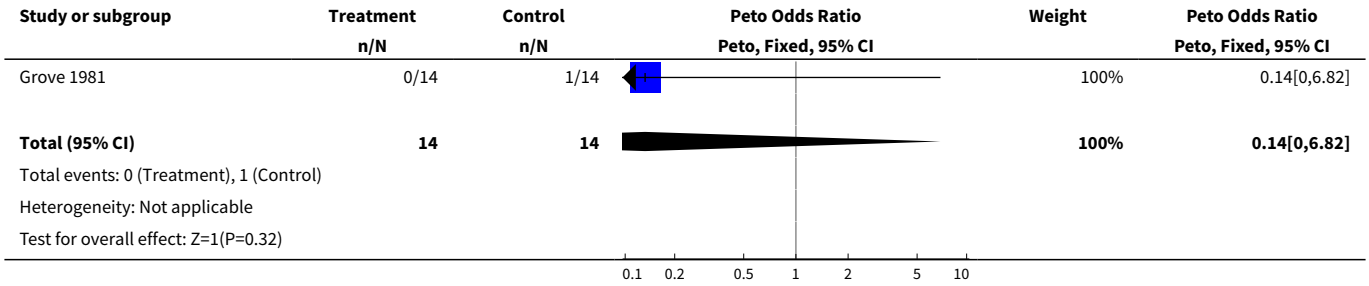
Analysis 4.1. Comparison 4 Musculoskeletal pain, Outcome 1 Lower limb pain 2 years.



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



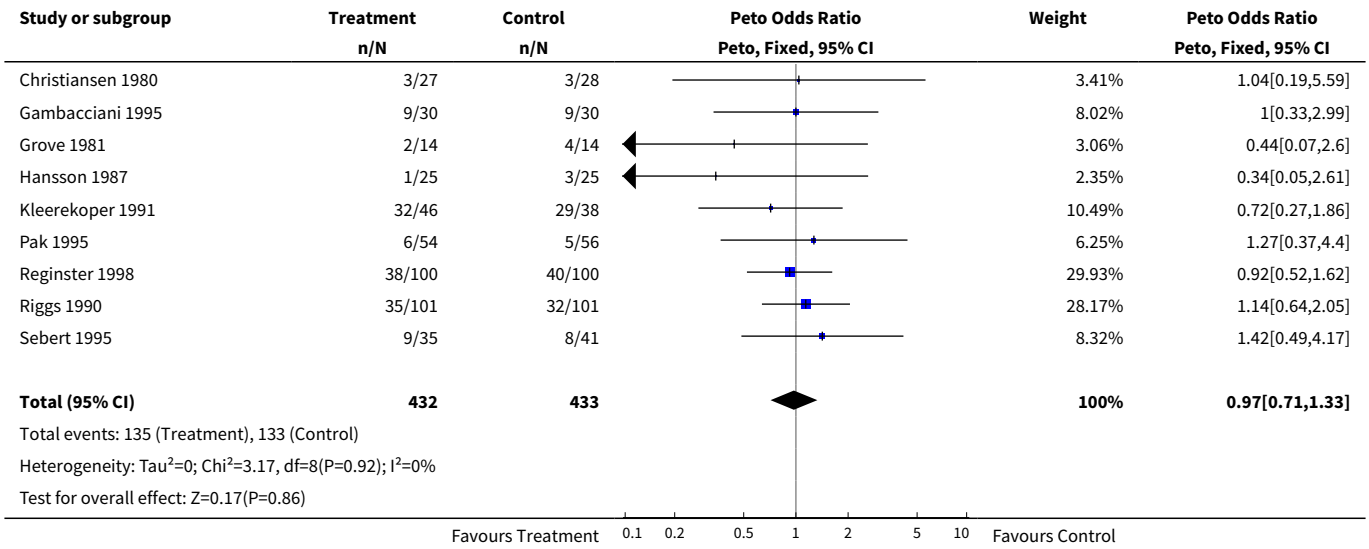
Analysis 4.3. Comparison 4 Musculoskeletal pain, Outcome 3 Finger paresthesia.



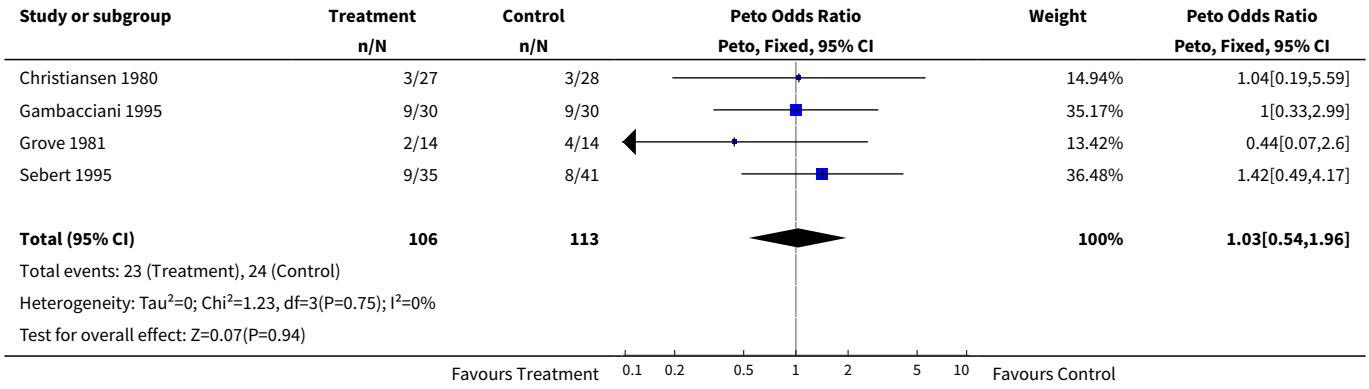
Comparison 5. Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of participants	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]

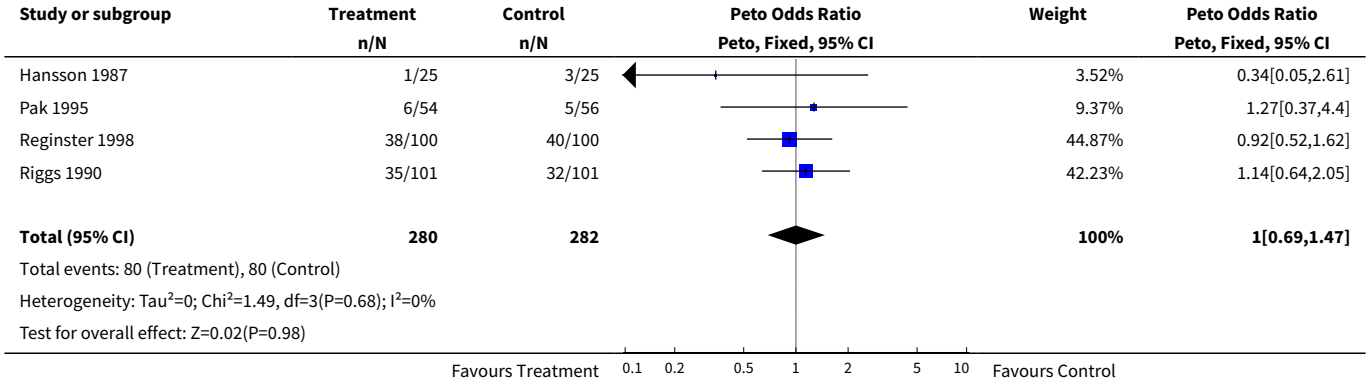
Analysis 5.1. Comparison 5 Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts overall.



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



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



Comparison 6. Subgroup Analysis: Type of Fluoride

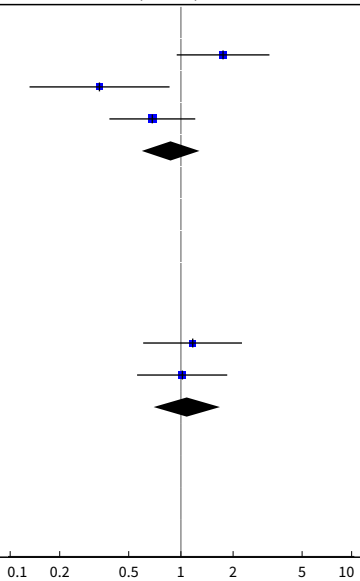
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	1033	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.72, 1.28]
1.1 NaF	3	531	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.60, 1.28]
1.2 MFP	2	502	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.70, 1.68]
2 No. People with new vertebral fractures 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]

Outcome or subgroup title	No. of studies	No. of participants	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 fractures 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 fractures 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]

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.

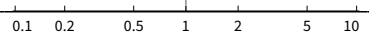
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.1.1 NaF					
Meunier 1998	27/73	37/146		21.94%	1.75[0.95,3.24]
Pak 1995	6/54	16/56		9.63%	0.34[0.13,0.86]
Riggs 1990	33/101	42/101		25.7%	0.68[0.39,1.21]
Subtotal (95% CI)	**228**	**303**		**57.26%**	**0.87[0.6,1.28]**
Total events: 66 (Treatment), 95 (Control)					
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)					
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 (Control)					
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)					



Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total (95% CI)	**397**	**636**		**100%**	**0.96[0.72,1.28]**
Total events: 106 (Treatment), 170 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.2, df=4(P=0.04); I^2=60.78%					
Test for overall effect: Z=0.31(P=0.76)					
Test for subgroup differences: Chi^2=0.53, df=1 (P=0.47), I^2=0%					

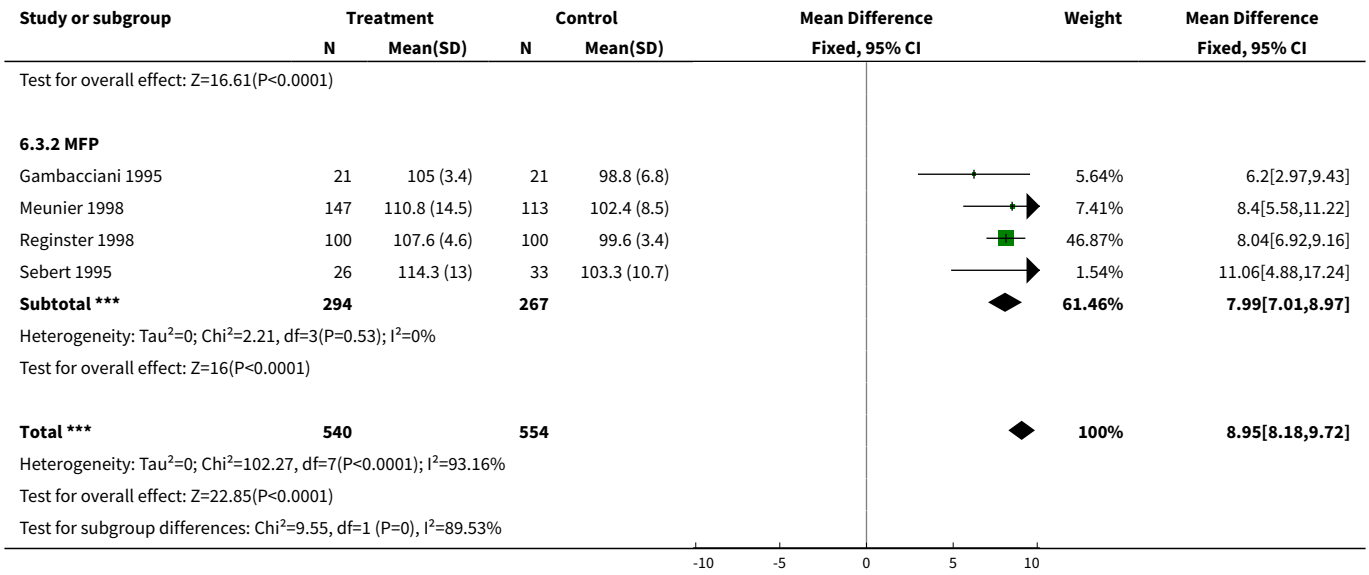
Analysis 6.2. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 2 No. People with new vertebral fractures 4 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (Control)					
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)					
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 (Control)					
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 (Control)					
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=6.53, df=1 (P=0.01), I^2=84.68%					



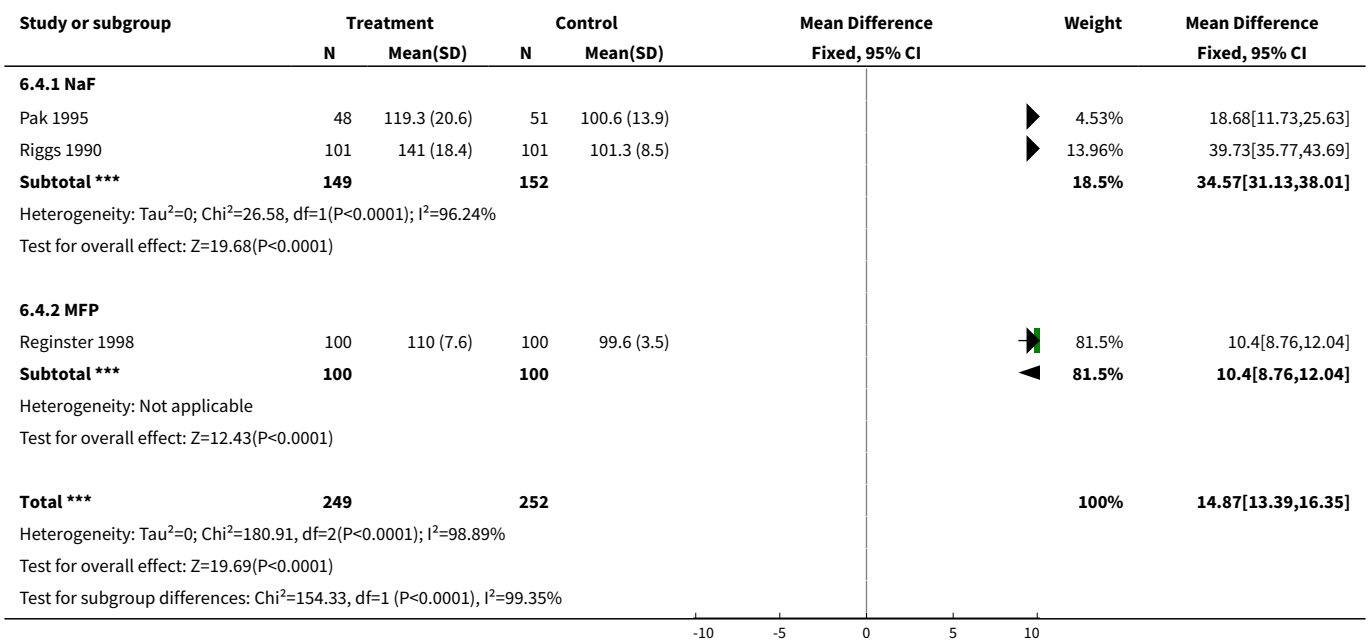
Analysis 6.3. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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<0.0001); I^2=96.69%							



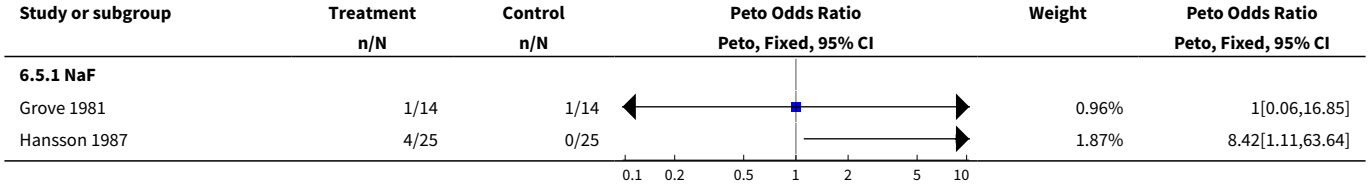
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=16.61(P<0.0001)							
6.3.2 MFP							
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		5.64%	6.2[2.97,9.43]
Meunier 1998	147	110.8 (14.5)	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); 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, df=7(P<0.0001); I^2=93.16%							
Test for overall effect: Z=22.85(P<0.0001)							
Test for subgroup differences: Chi^2=9.55, df=1 (P=0), I^2=89.53%							

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

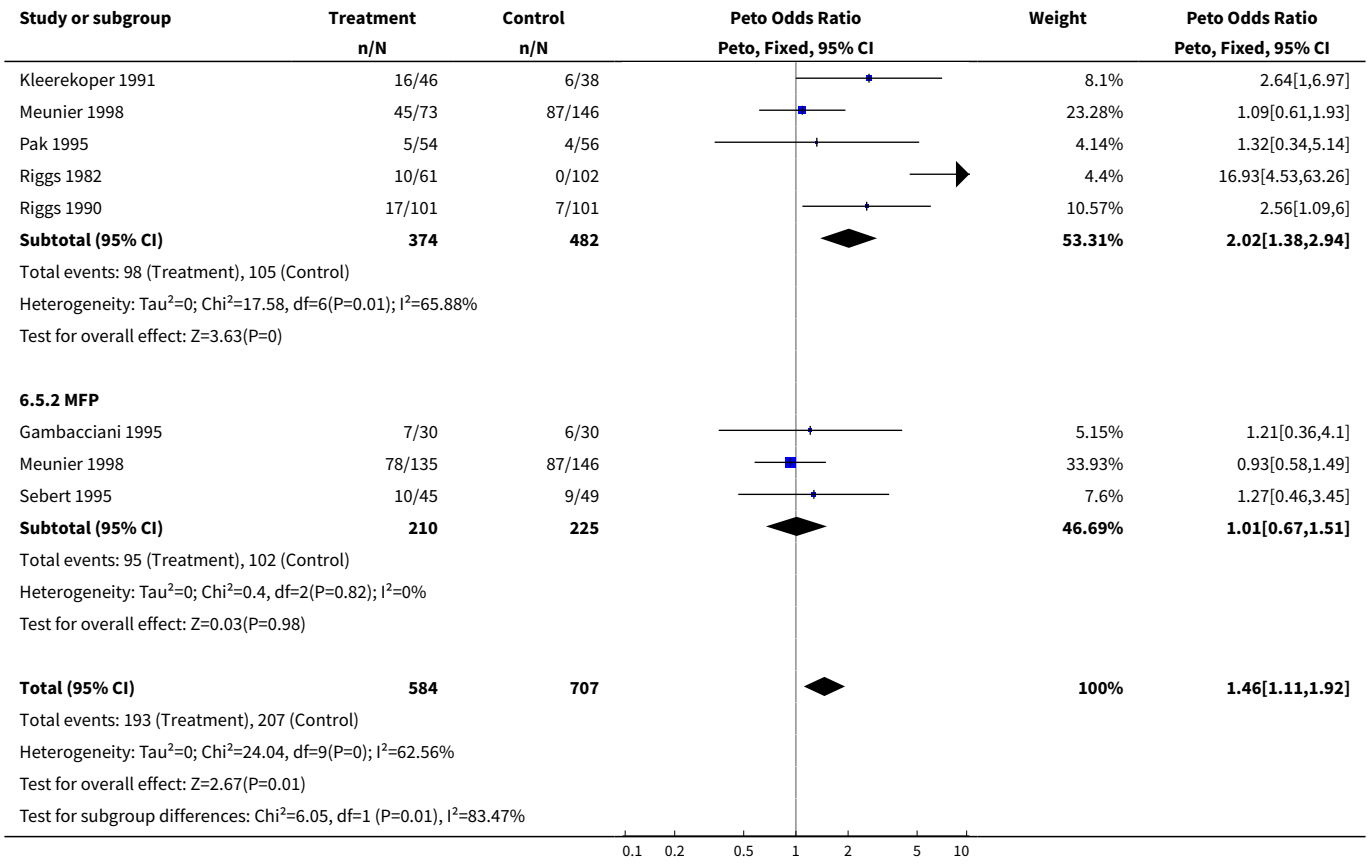


Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.4.1 NaF							
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)		4.53%	18.68[11.73,25.63]
Riggs 1990	101	141 (18.4)	101	101.3 (8.5)		13.96%	39.73[35.77,43.69]
Subtotal ***	**149**		**152**			**18.5%**	**34.57[31.13,38.01]**
Heterogeneity: Tau^2=0; Chi^2=26.58, df=1(P<0.0001); I^2=96.24%							
Test for overall effect: Z=19.68(P<0.0001)							
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<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau^2=0; Chi^2=180.91, df=2(P<0.0001); I^2=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi^2=154.33, df=1 (P<0.0001), I^2=99.35%							

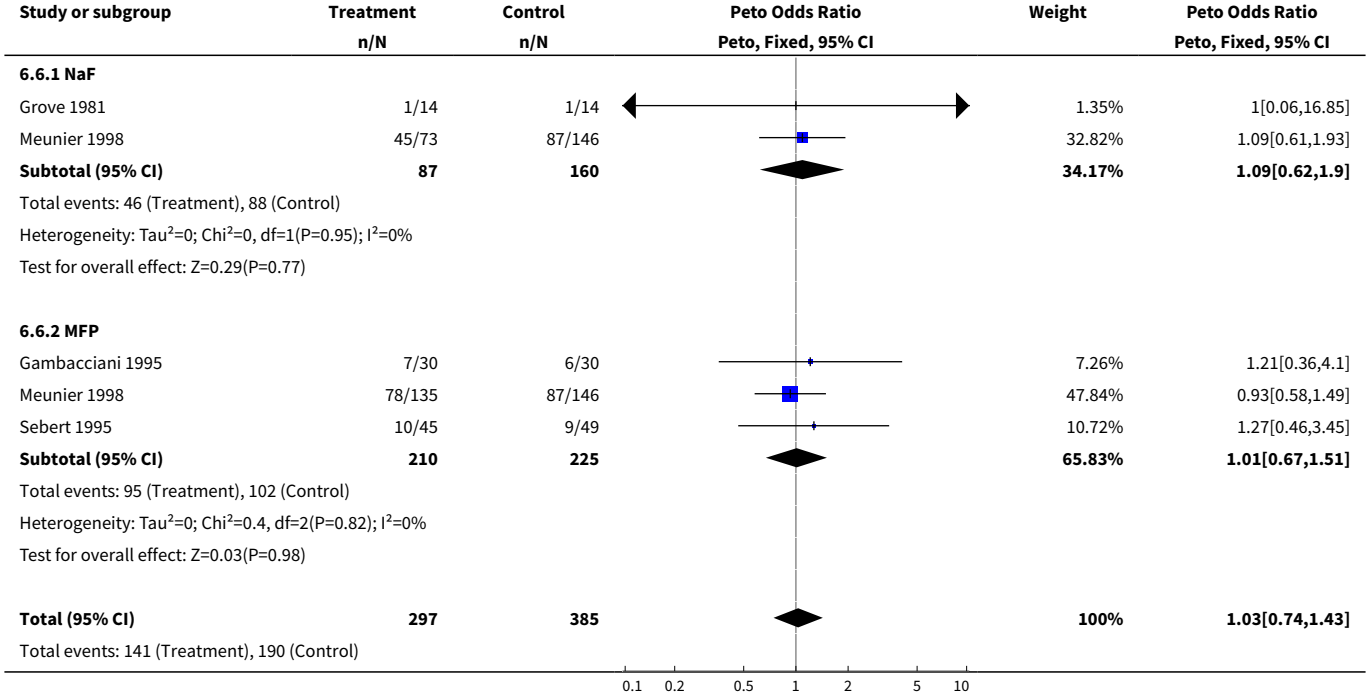
Analysis 6.5. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 5 GI minor overall.



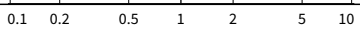
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.5.1 NaF					
Grove 1981	1/14	1/14		0.96%	1[0.06,16.85]
Hansson 1987	4/25	0/25		1.87%	8.42[1.11,63.64]



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

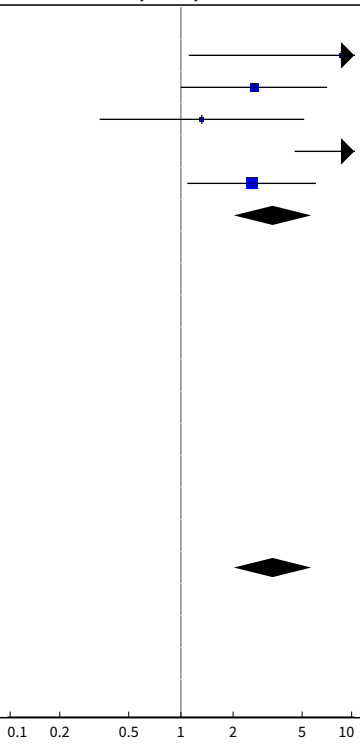


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.45, df=4(P=0.98); I²=0%					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi²=0.05, df=1 (P=0.83), I²=0%					



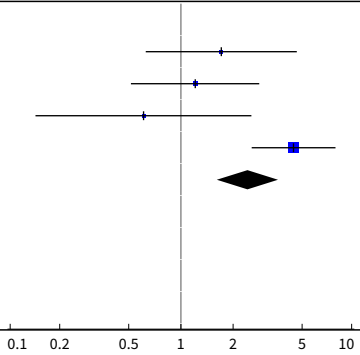
Analysis 6.7. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 7 GI minor 4 years.

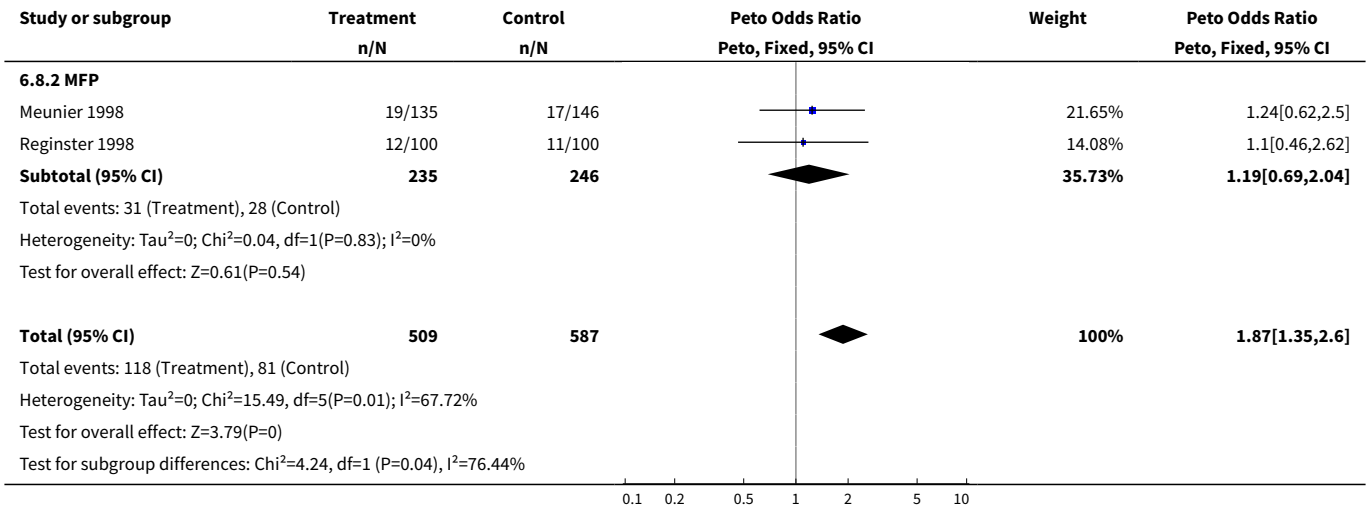
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.7.1 NaF					
Hansson 1987	4/25	0/25		6.42%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		27.85%	2.64[1,6.97]
Pak 1995	5/54	4/56		14.26%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		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 (Control)					
Heterogeneity: Tau²=0; Chi²=9.02, df=4(P=0.06); I²=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 (Control)					
Heterogeneity: Tau²=0; Chi²=9.02, df=4(P=0.06); I²=55.64%					
Test for overall effect: Z=4.65(P<0.0001)					
Test for subgroup differences: Not applicable					



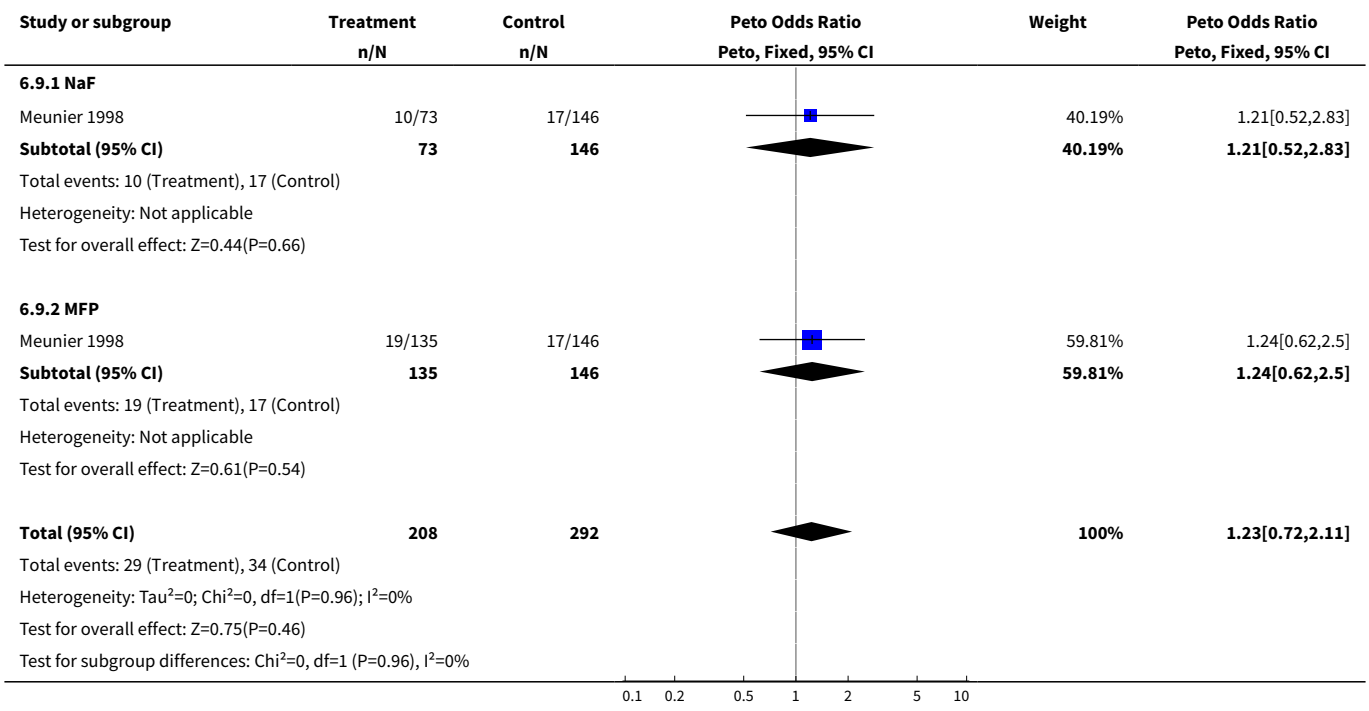
Analysis 6.8. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 8 Non vertebral fractures overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 (Control)					
Heterogeneity: Tau²=0; Chi²=11.2, df=3(P=0.01); I²=73.22%					
Test for overall effect: Z=4.27(P<0.0001)					

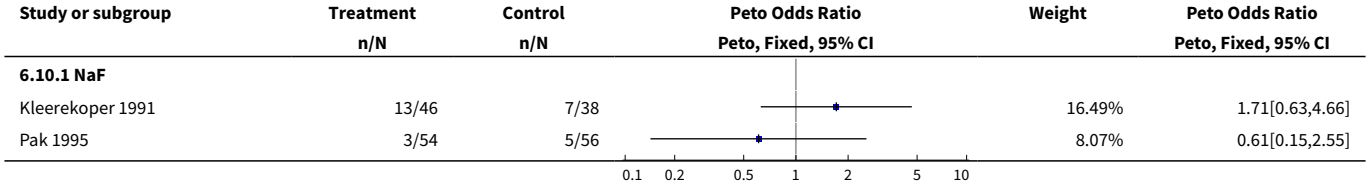


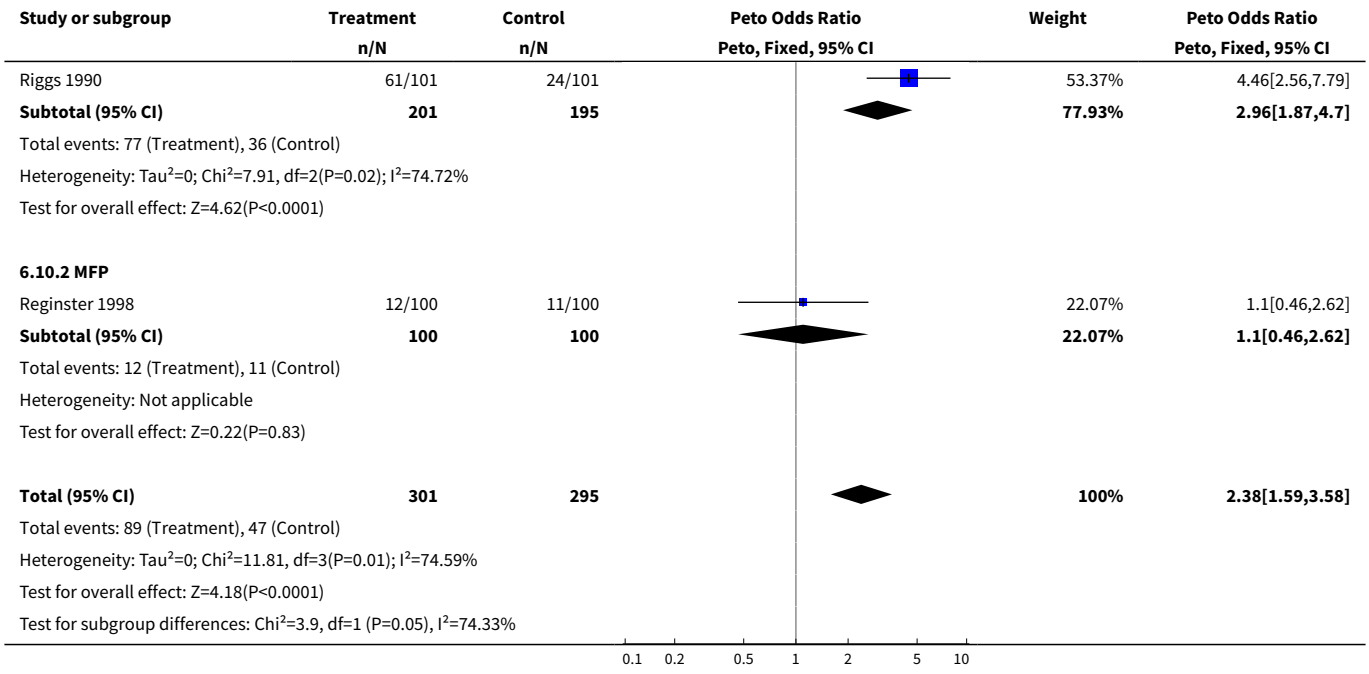


Analysis 6.9. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 9 Non vertebral fractures 2 years.

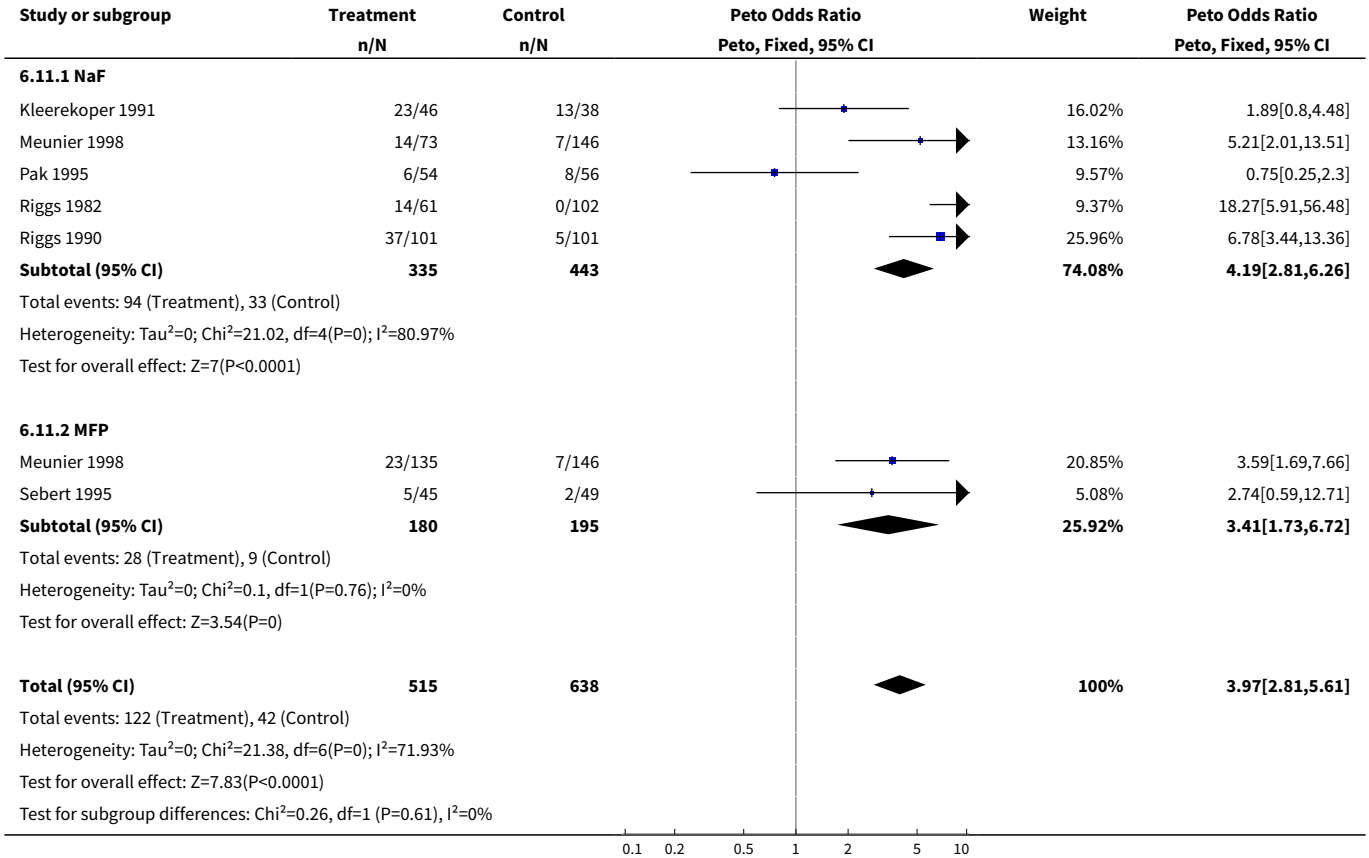


Analysis 6.10. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 10 Non vertebral fractures 4 years.

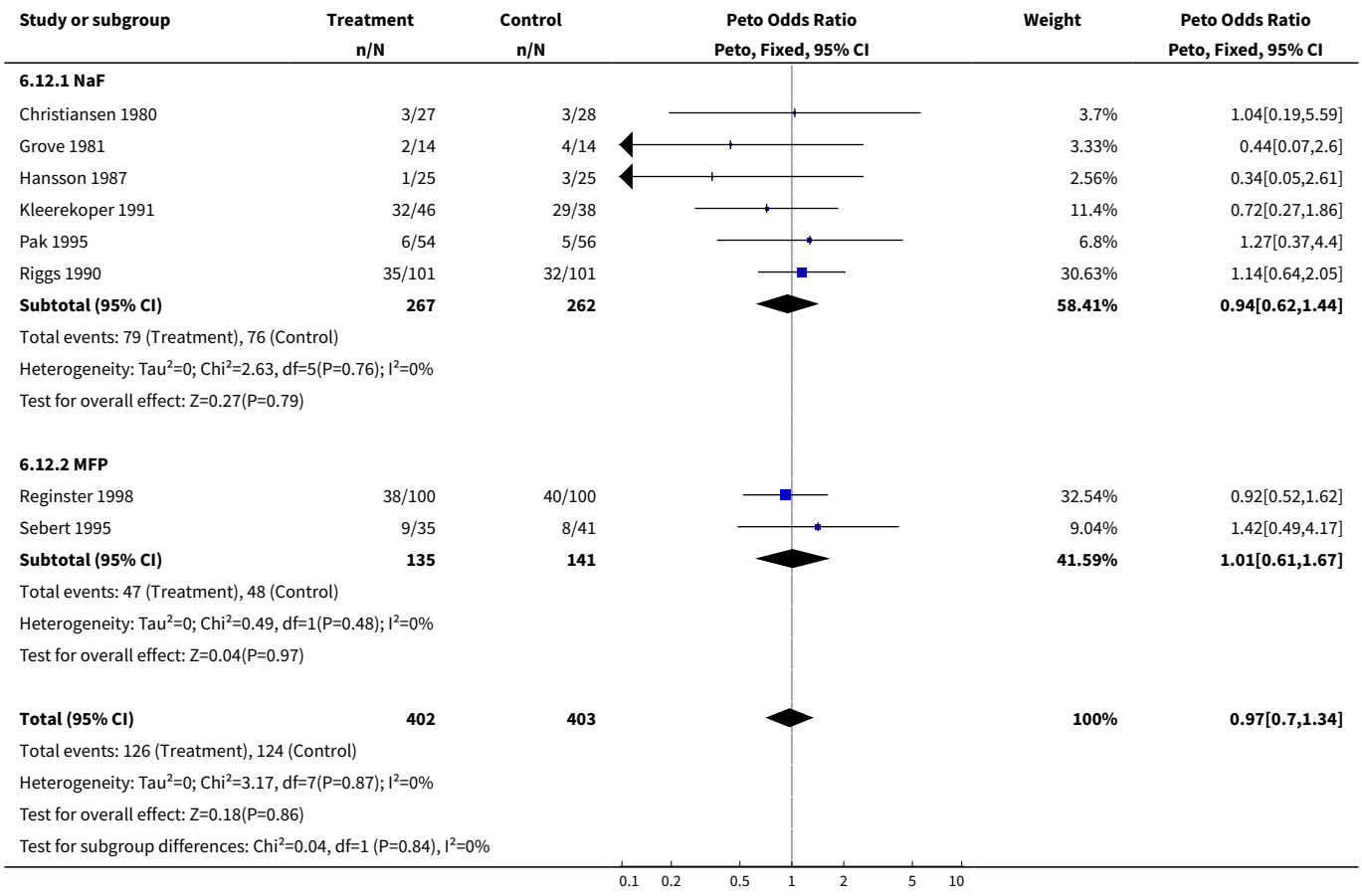




Analysis 6.11. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 11 Lower limb pain syndrome.

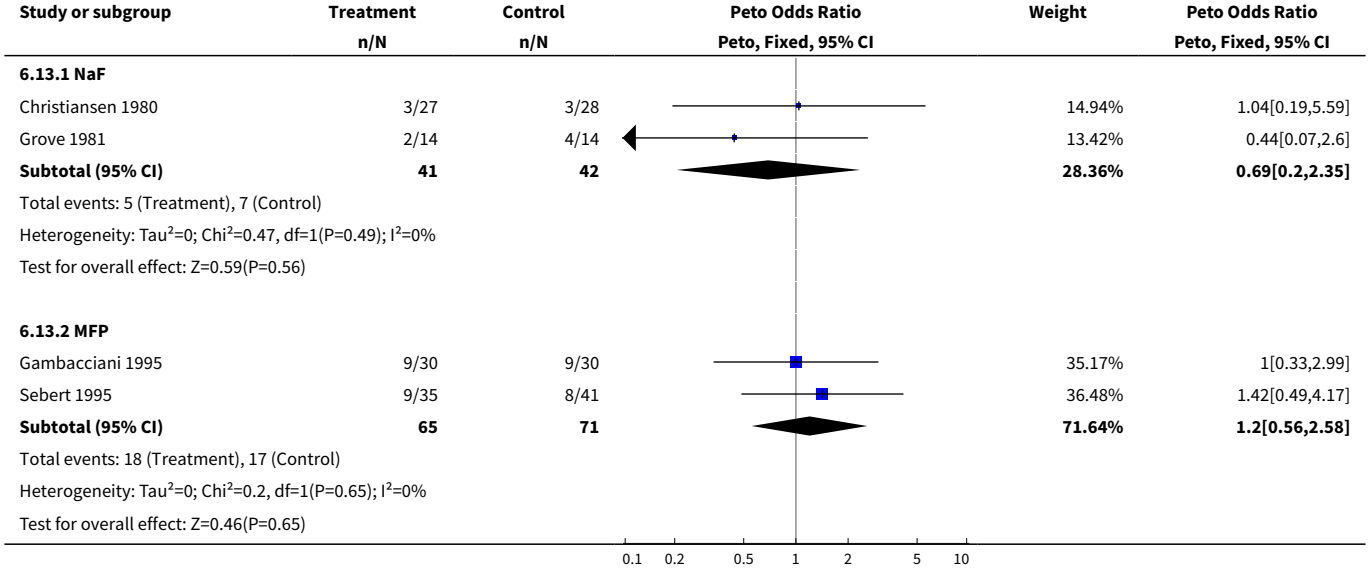


Analysis 6.12. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 12 Withdrawals and dropouts overall.

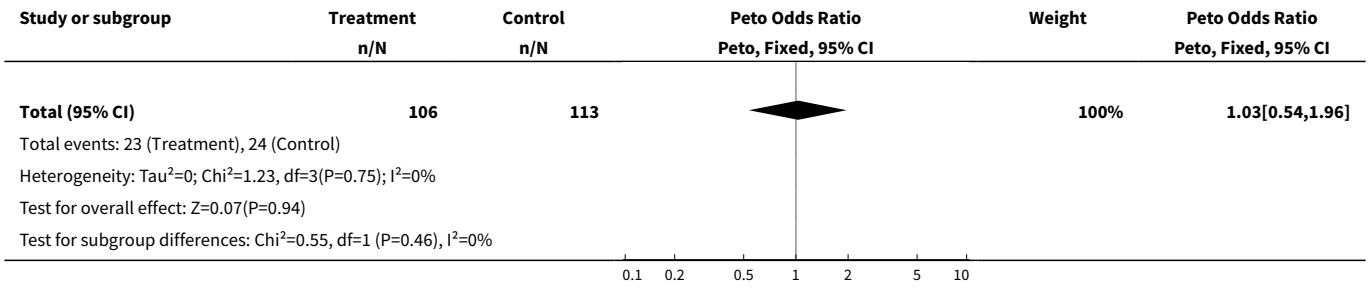


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.12.1 NaF					
Christiansen 1980	3/27	3/28		3.7%	1.04[0.19,5.59]
Grove 1981	2/14	4/14		3.33%	0.44[0.07,2.6]
Hansson 1987	1/25	3/25		2.56%	0.34[0.05,2.61]
Kleerekoper 1991	32/46	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 (Control)					
Heterogeneity: Tau²=0; Chi²=2.63, df=5(P=0.76); I²=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 (Control)					
Heterogeneity: Tau²=0; Chi²=0.49, df=1(P=0.48); I²=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 (Control)					
Heterogeneity: Tau²=0; Chi²=3.17, df=7(P=0.87); I²=0%					
Test for overall effect: Z=0.18(P=0.86)					
Test for subgroup differences: Chi²=0.04, df=1 (P=0.84), I²=0%					

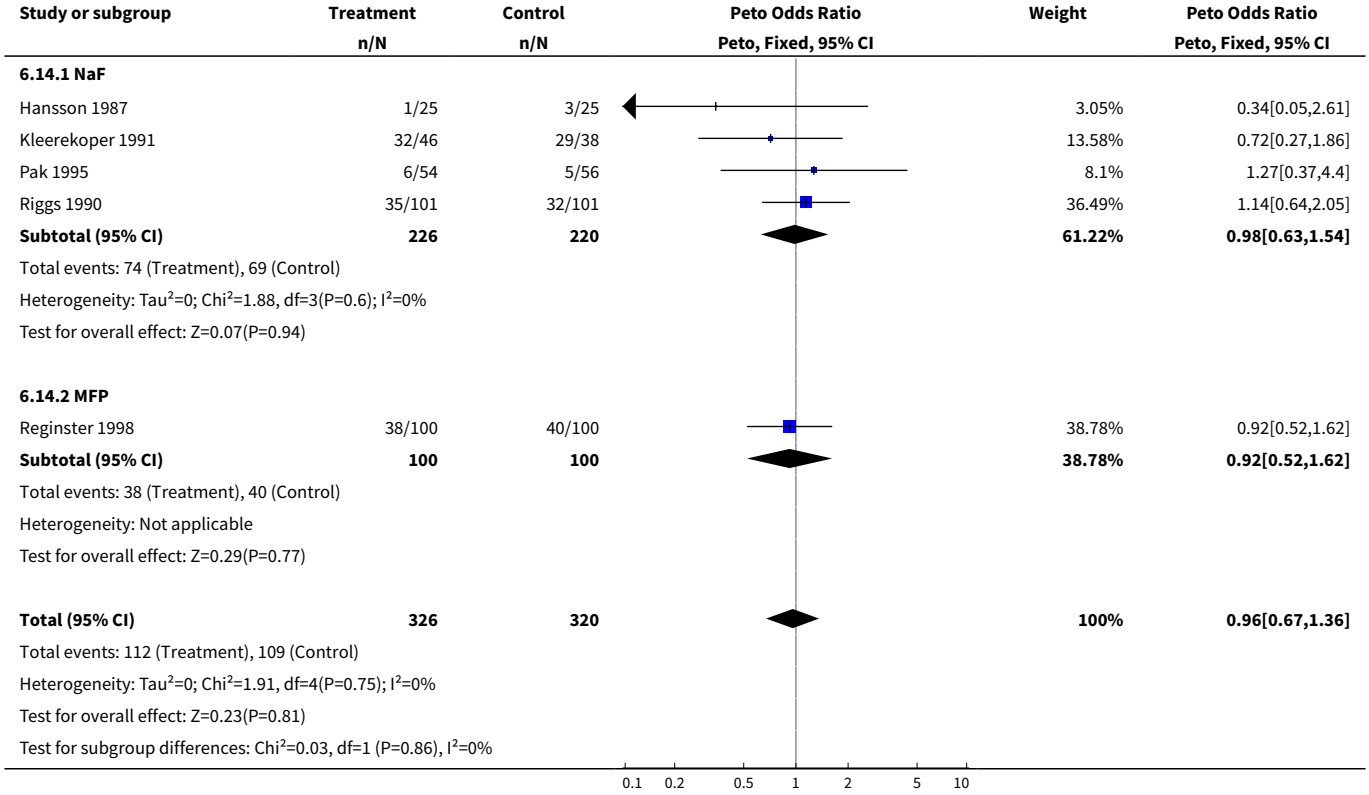
Analysis 6.13. Comparison 6 Subgroup Analysis: Type of Fluoride, Outcome 13 Withdrawals and dropouts 2 years.



Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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: Tau²=0; Chi²=0.47, df=1(P=0.49); I²=0%					
Test for overall effect: Z=0.59(P=0.56)					
6.13.2 MFP					
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 (Control)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%					
Test for overall effect: Z=0.46(P=0.65)					



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



Comparison 7. Sensitivity Dosage: Fluoride vs Placebo

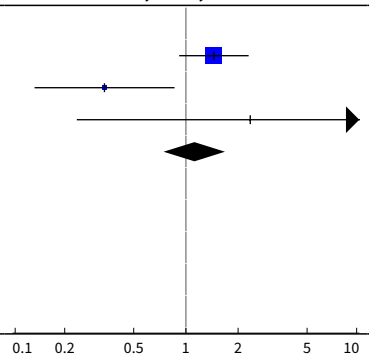
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 Low dose	3	540	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.74, 1.68]
1.2 High dose	1	202	Peto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

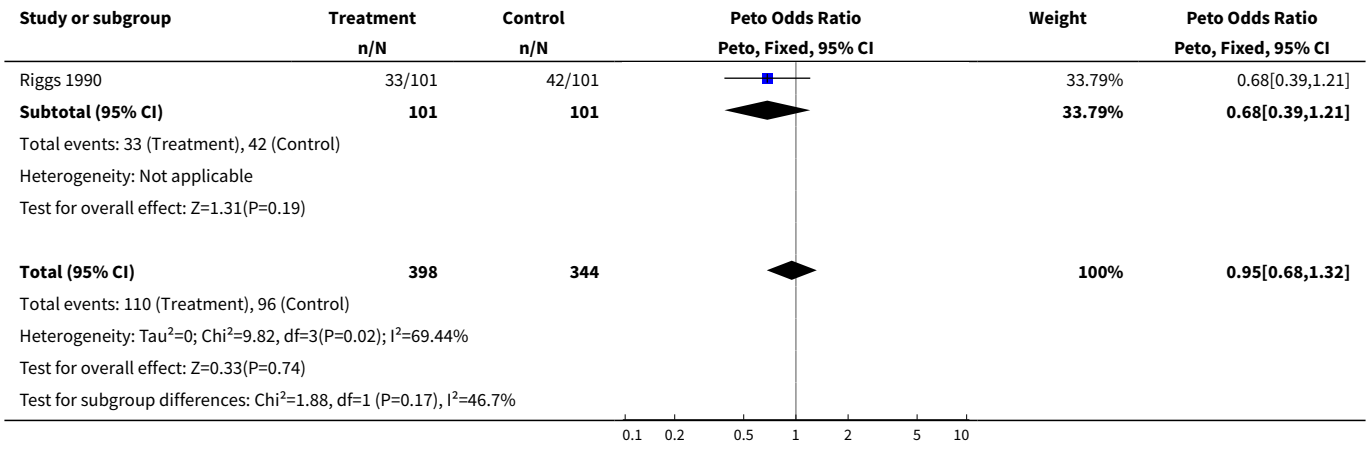
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 No. People with new vertebral fractures 4 years	5	646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.94]
2.1 Low dose	3	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.24 [0.12, 0.49]
2.2 High dose	2	286	Peto 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 fractures 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 fractures 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]

Outcome or subgroup title	No. of studies	No. of participants	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 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 syndrome	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% CI)	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]

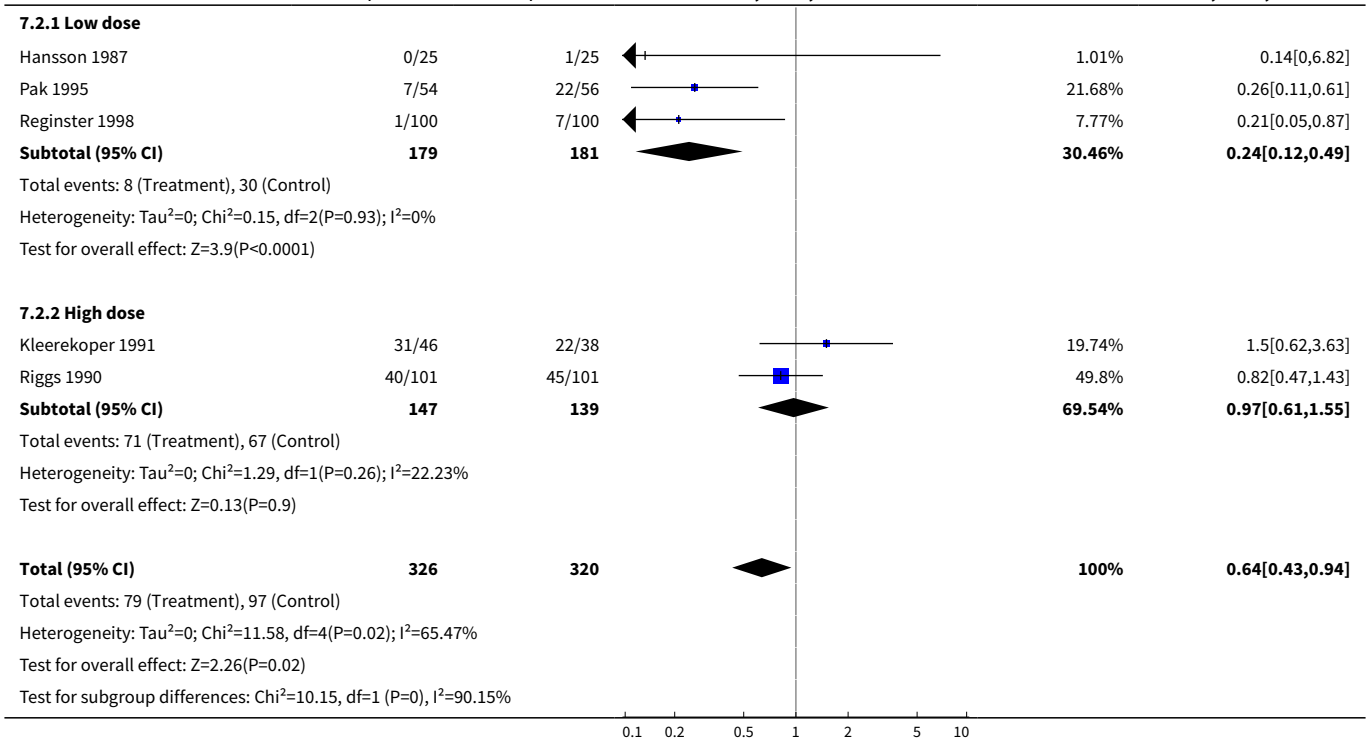
Analysis 7.1. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.1.1 Low dose					
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]
Sebert 1995	2/35	1/41		2.07%	2.35[0.23,23.42]
Subtotal (95% CI)	**297**	**243**		**66.21%**	**1.12[0.74,1.68]**
Total events: 77 (Treatment), 54 (Control)					
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					



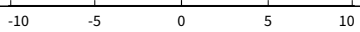


Analysis 7.2. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 2 No. People with new vertebral fractures 4 years.



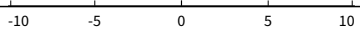
Analysis 7.3. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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<0.0001)							
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<0.0001)							
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<0.0001)							
Test for subgroup differences: Chi^2=89.05, df=1 (P<0.0001), I^2=98.88%							



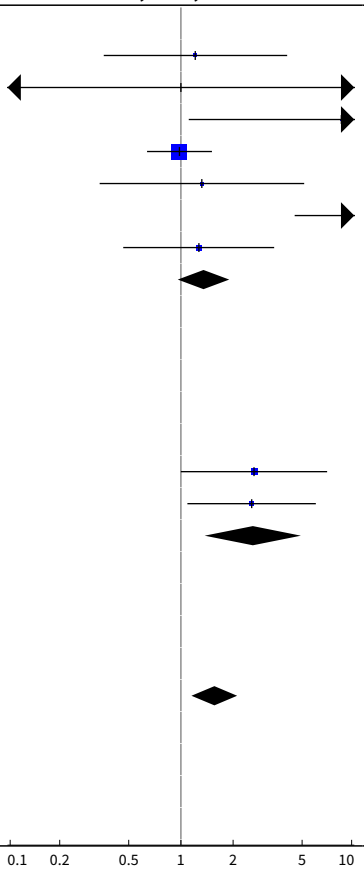
Analysis 7.4. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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); I^2=80.62%							
Test for overall effect: Z=13.31(P<0.0001)							
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<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau^2=0; Chi^2=180.91, df=2(P<0.0001); I^2=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi^2=175.75, df=1 (P<0.0001), I^2=99.43%							



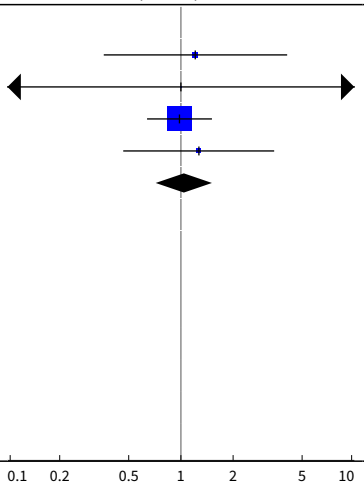
Analysis 7.5. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 5 GI minor overall.

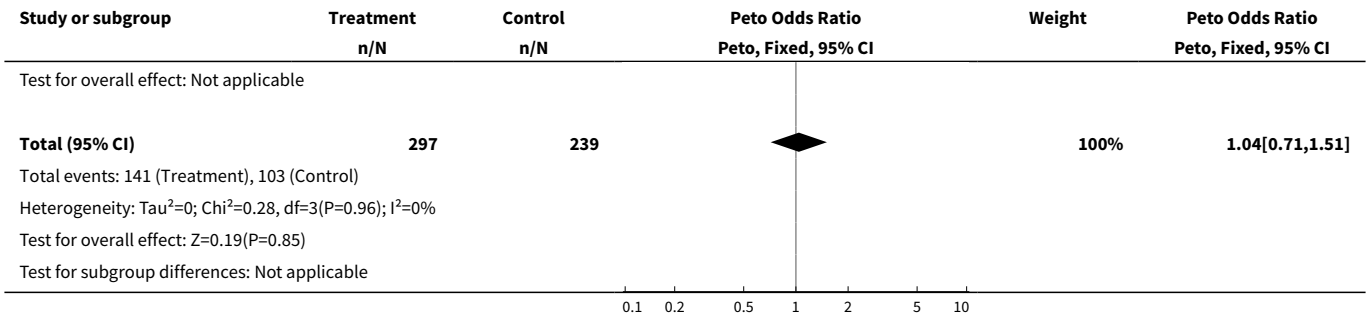
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.5.1 Low dose					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14		1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25		2.22%	8.42[1.11,63.64]
Meunier 1998	123/208	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 (Control)					
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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^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 (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=3.13, df=1 (P=0.08), I^2=68.01%					



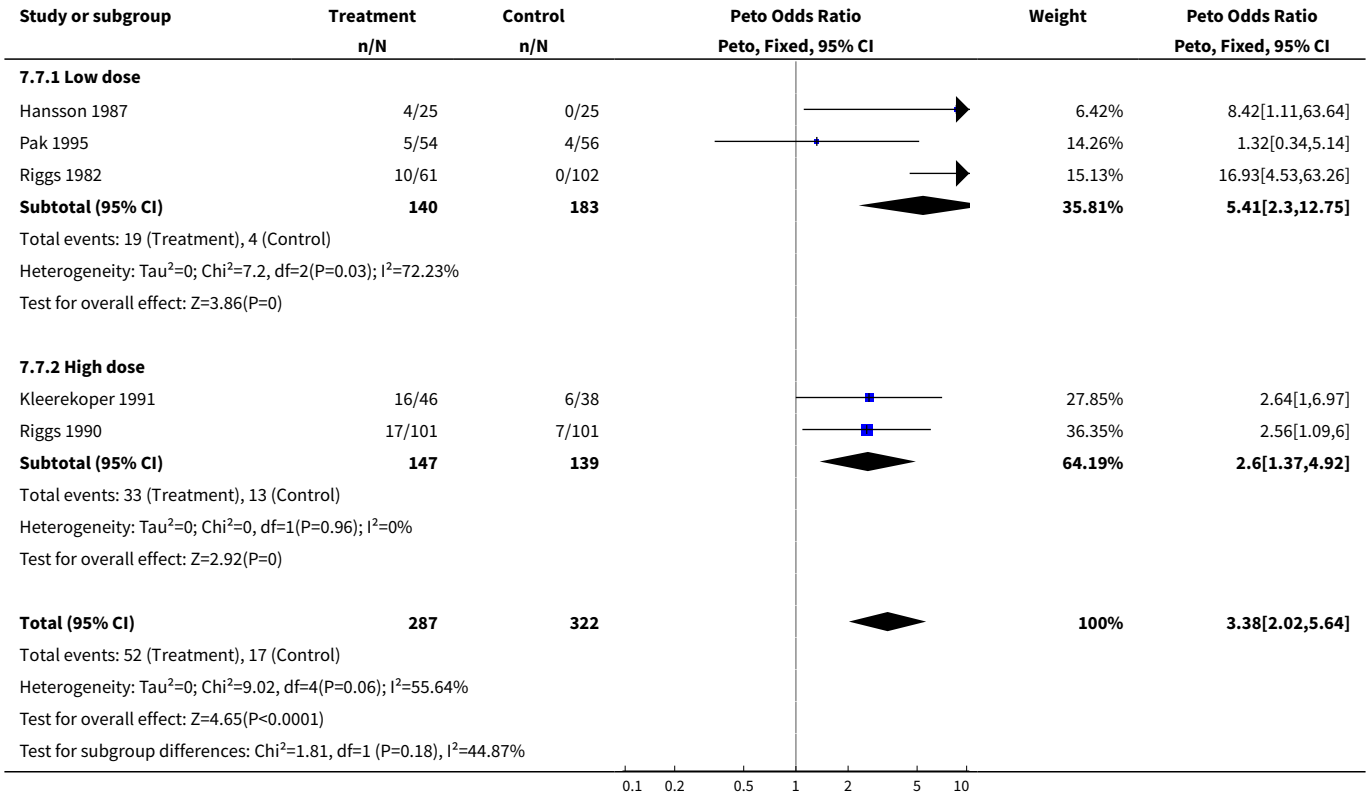
Analysis 7.6. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (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 (Control)					
Heterogeneity: Not applicable					

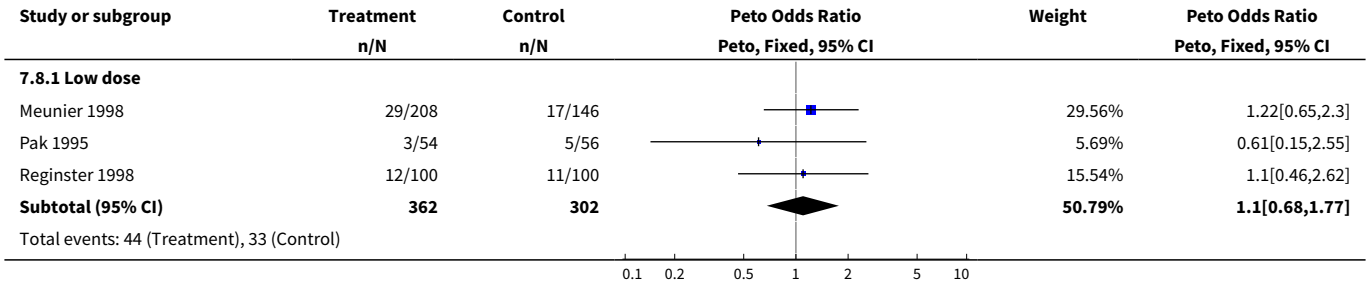


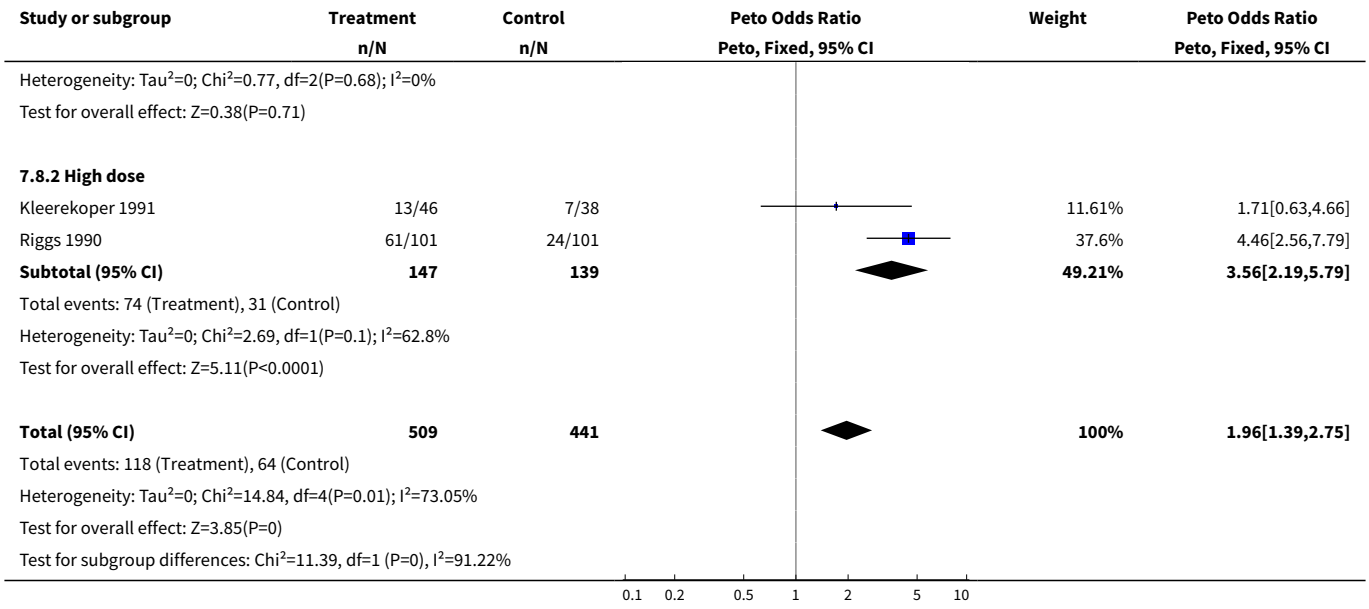


Analysis 7.7. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 7 GI minor 4 years.

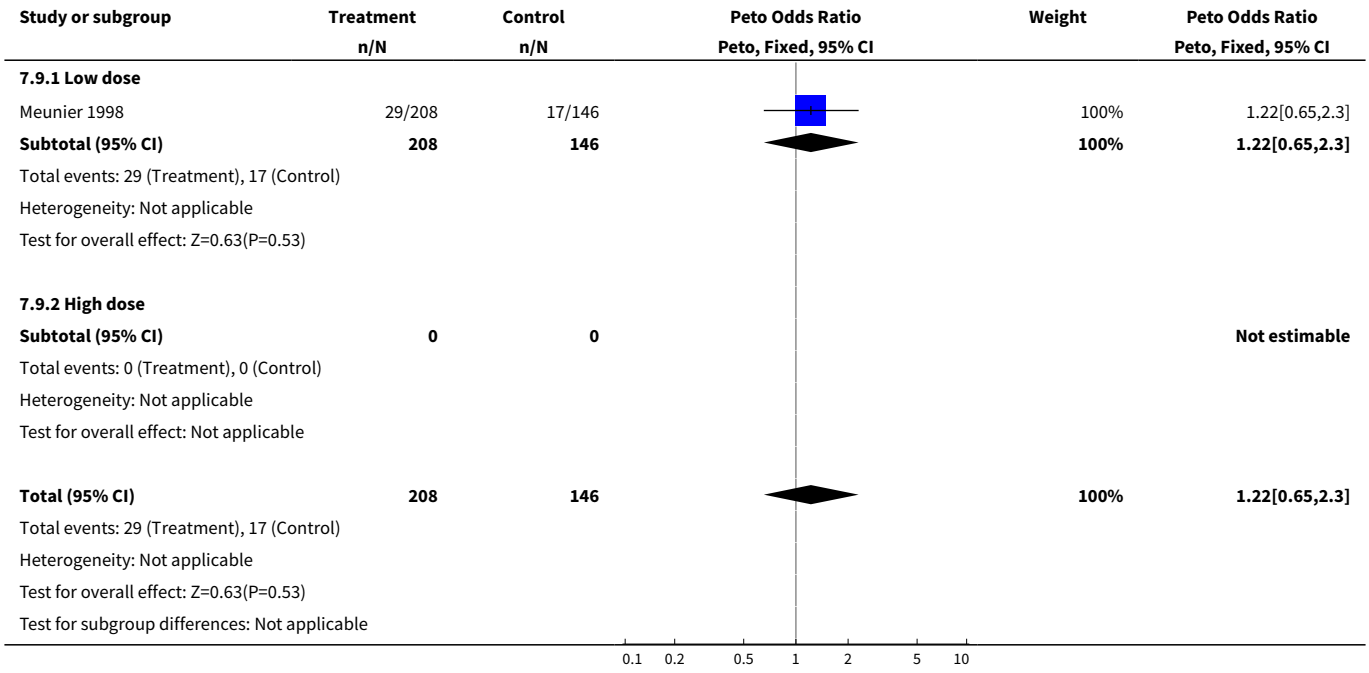


Analysis 7.8. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 8 Non vertebral fractures overall.

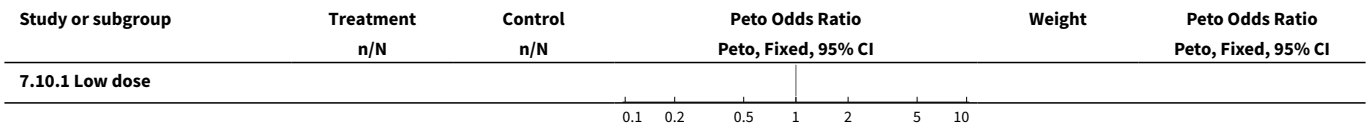


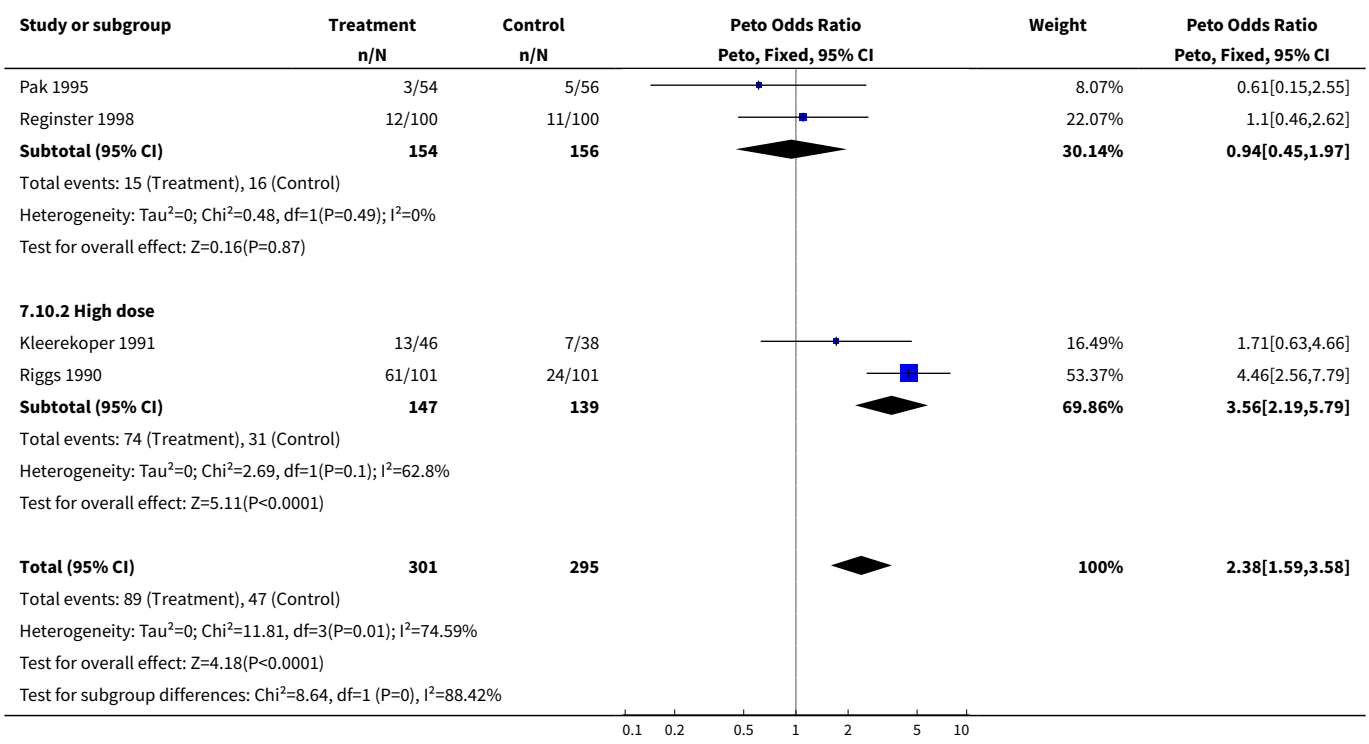


Analysis 7.9. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 9 Non vertebral fractures 2 years.

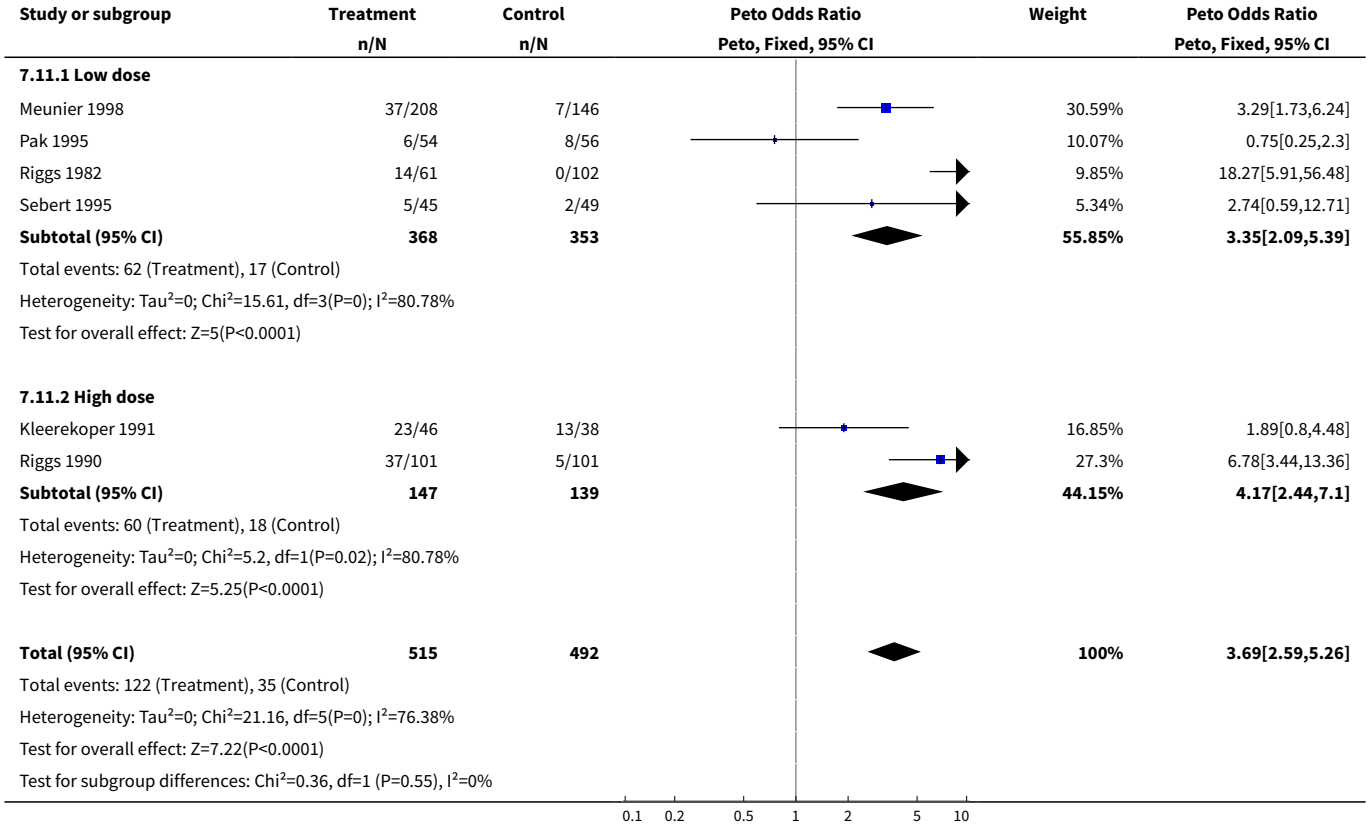


Analysis 7.10. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 10 Non vertebral fractures 4 years.



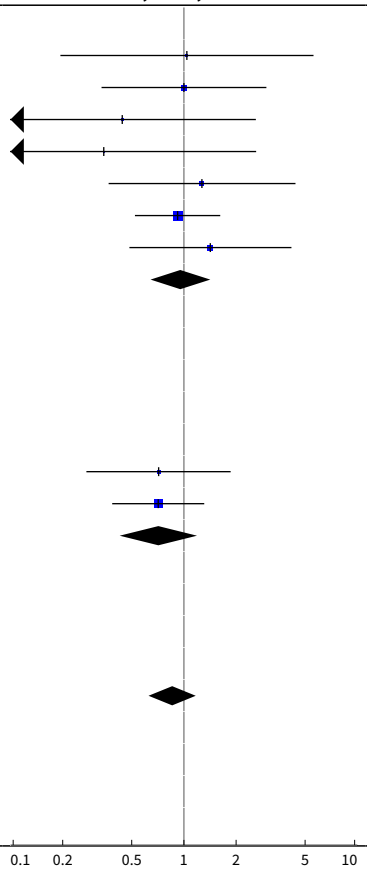


Analysis 7.11. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 11 Lower limb pain syndrome.



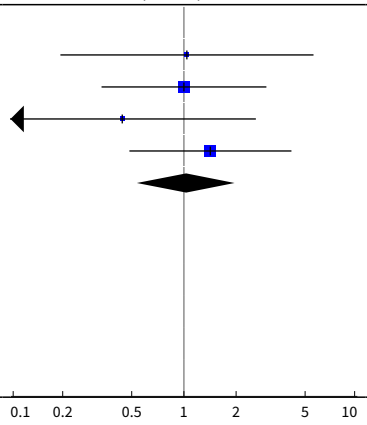
Analysis 7.12. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 12 Withdrawals and dropouts overall.

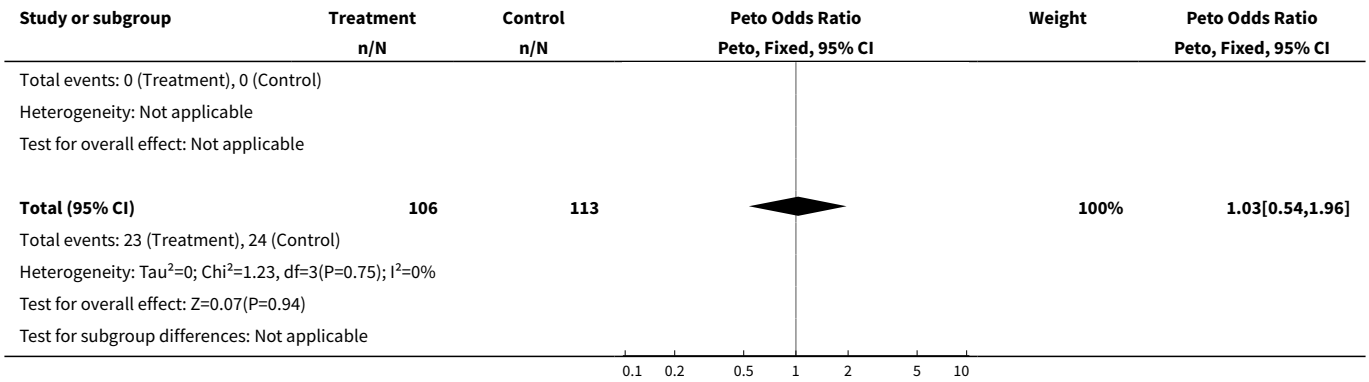
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.12.1 Low dose					
Christiansen 1980	3/27	3/28		3.49%	1.04[0.19,5.59]
Gambacciani 1995	9/30	9/30		8.22%	1[0.33,2.99]
Grove 1981	2/14	4/14		3.14%	0.44[0.07,2.6]
Hansson 1987	1/25	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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.47, df=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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.24, df=8(P=0.92); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi^2=0.77, df=1 (P=0.38), I^2=0%					



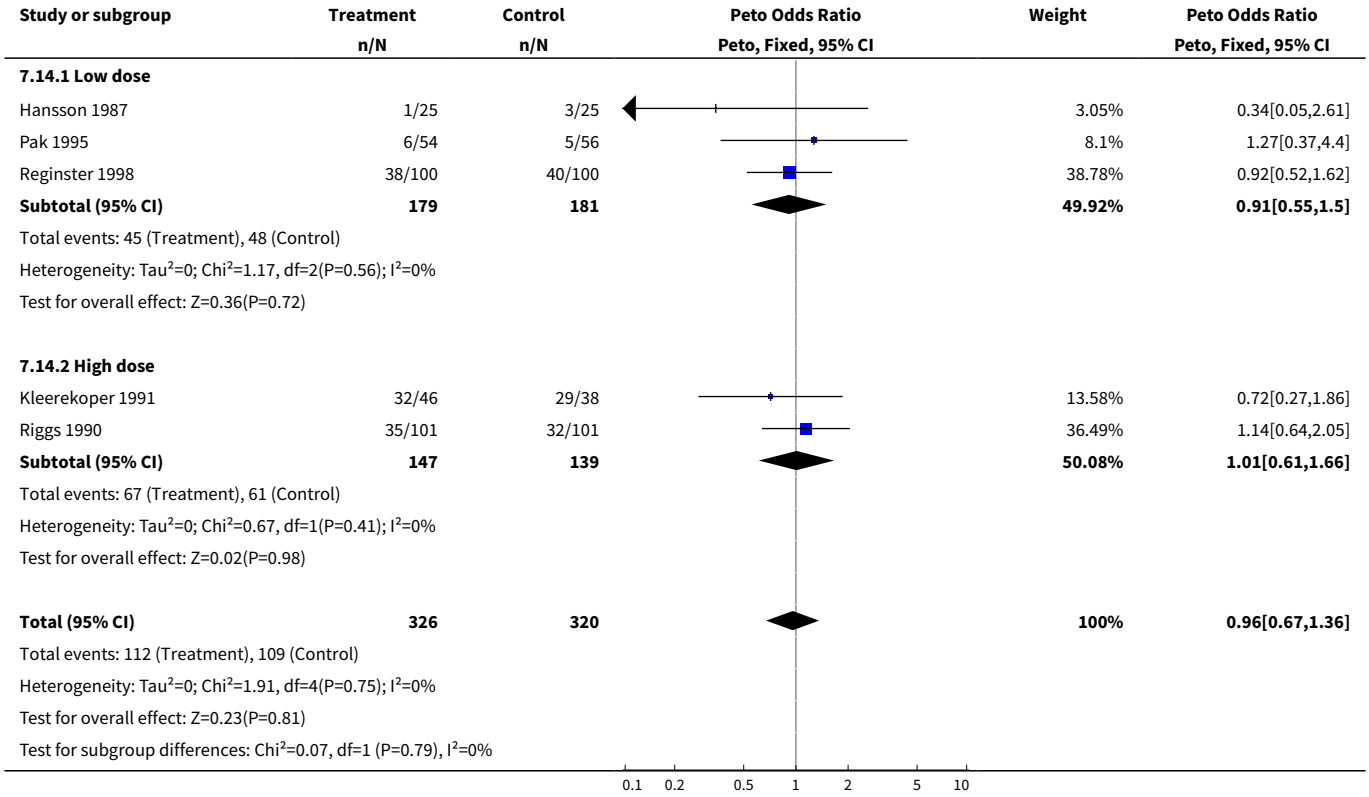
Analysis 7.13. Comparison 7 Sensitivity Dosage: Fluoride vs Placebo, Outcome 13 Withdrawals and dropouts 2 yeras.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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		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 (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)					
7.13.2 High dose					
Subtotal (95% CI)	**0**	**0**			**Not estimable**





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



Comparison 8. Sensitivity Quality

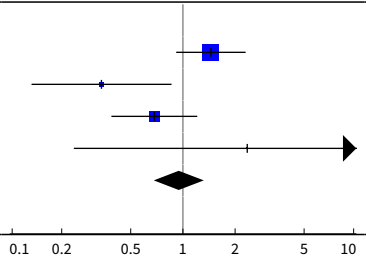
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

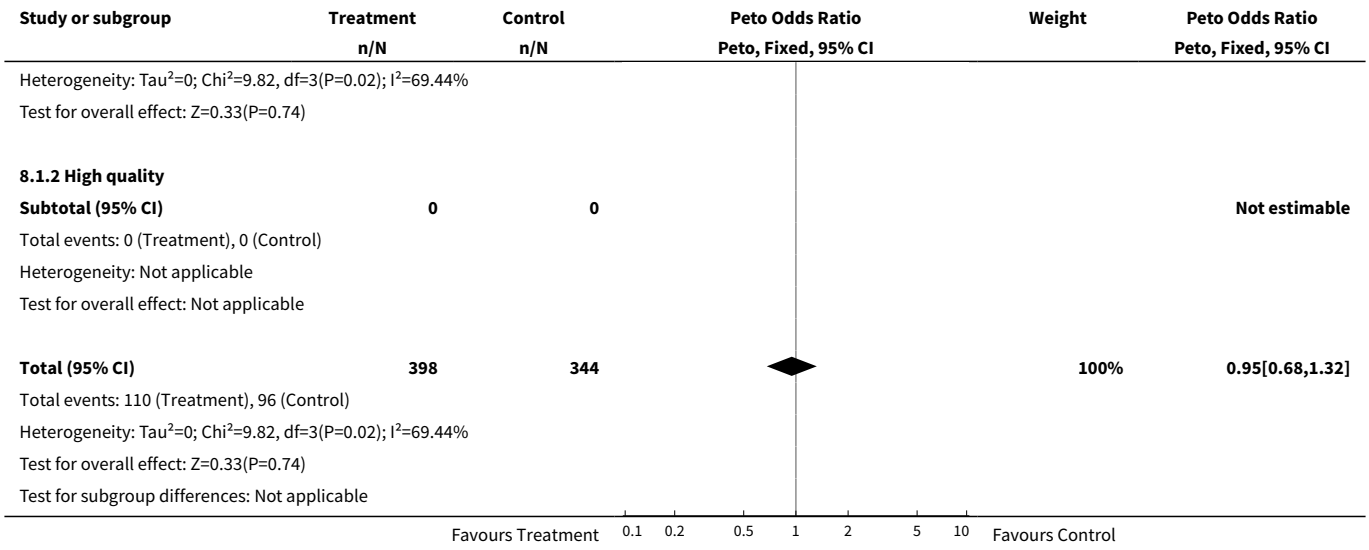
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Low quality	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.2 High quality	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 No. Peiple with new vertebral fractures 4 years	5	646	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]

Outcome or subgroup title	No. of studies	No. of participants	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 fractures 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 syndrome	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]

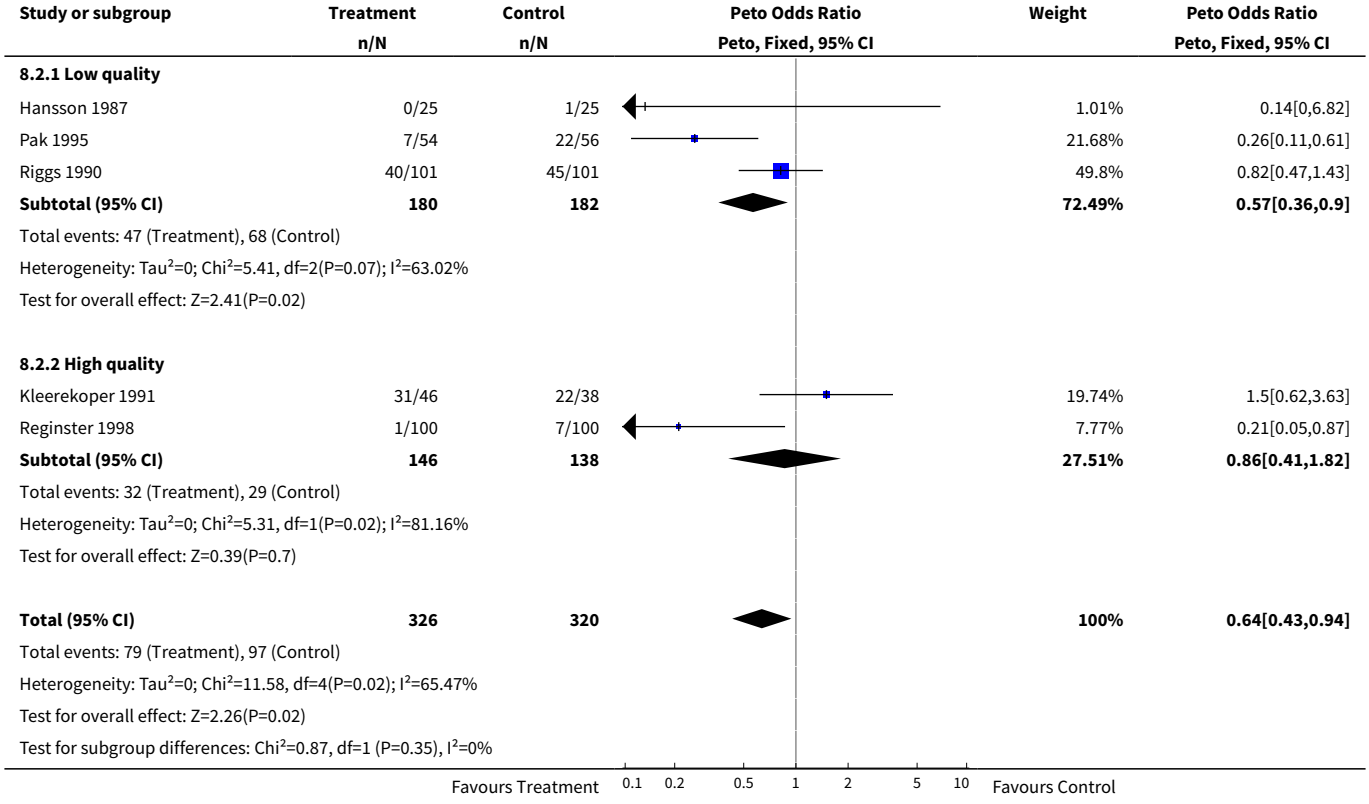
Analysis 8.1. Comparison 8 Sensitivity Quality, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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		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 (Control)					



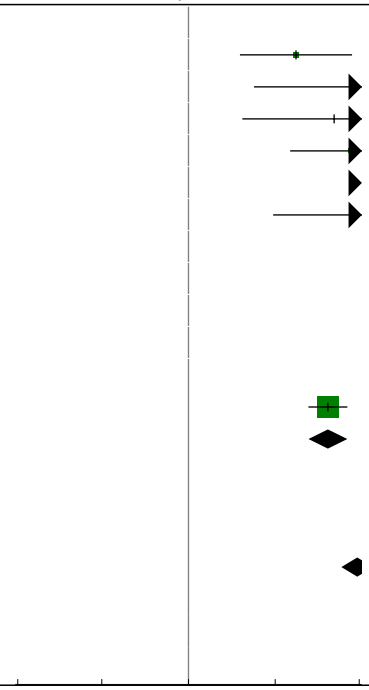


Analysis 8.2. Comparison 8 Sensitivity Quality, Outcome 2 No. Peiple with new vertebral fractures 4 years.



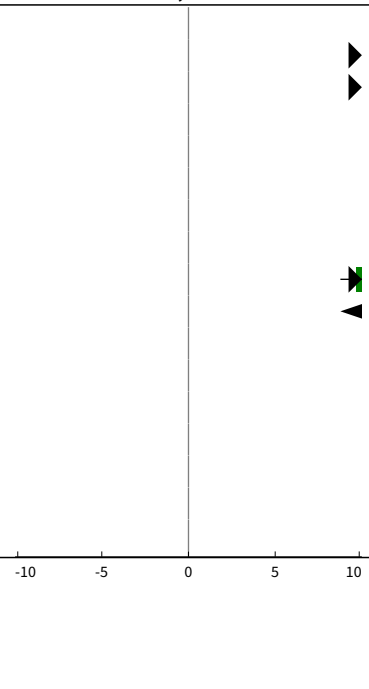
Analysis 8.3. Comparison 8 Sensitivity Quality, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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)		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]
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: Tau²=0; Chi²=66.28, df=5(P<0.0001); I²=92.46%							
Test for overall effect: Z=16.19(P<0.0001)							
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<0.0001)							
Total ***	**466**		**536**			**100%**	**9.73[8.82,10.65]**
Heterogeneity: Tau²=0; Chi²=92.68, df=6(P<0.0001); I²=93.53%							
Test for overall effect: Z=20.82(P<0.0001)							
Test for subgroup differences: Chi²=26.4, df=1 (P<0.0001), I²=96.21%							



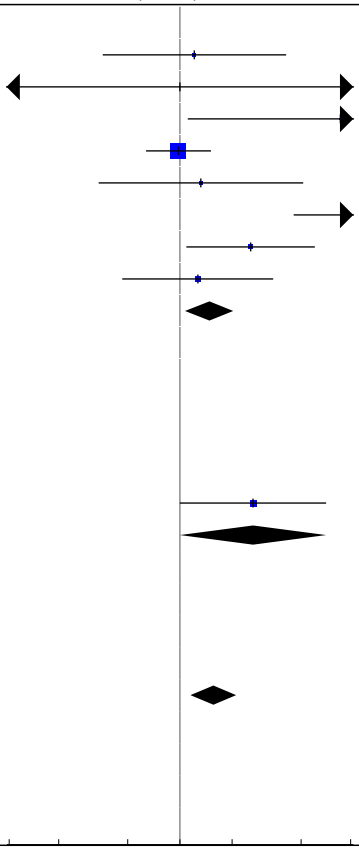
Analysis 8.4. Comparison 8 Sensitivity Quality, Outcome 4 Lumbar BMD % 4 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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: Tau²=0; Chi²=26.58, df=1(P<0.0001); I²=96.24%							
Test for overall effect: Z=19.68(P<0.0001)							
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<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau²=0; Chi²=180.91, df=2(P<0.0001); I²=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi²=154.33, df=1 (P<0.0001), I²=99.35%							



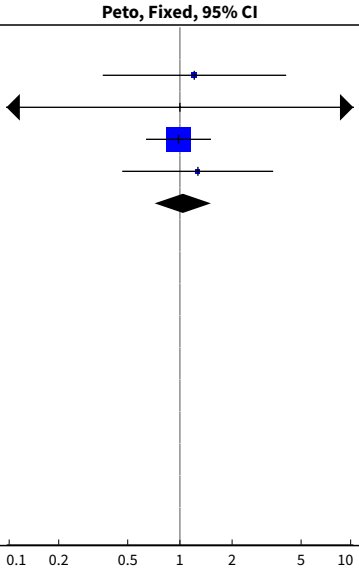
Analysis 8.5. Comparison 8 Sensitivity Quality, Outcome 5 GI minor overall.

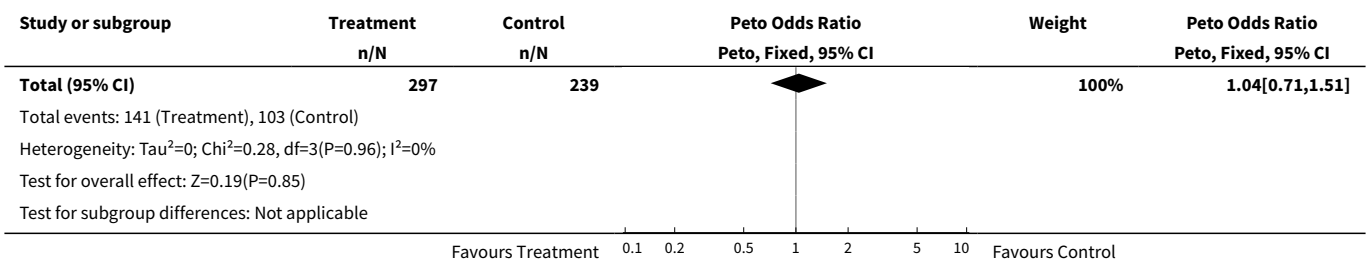
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
8.5.1 Low quality					
Gambacciani 1995	7/30	6/30		6.12%	1.21[0.36,4.1]
Grove 1981	1/14	1/14		1.14%	1[0.06,16.85]
Hansson 1987	4/25	0/25		2.22%	8.42[1.11,63.64]
Meunier 1998	123/208	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 (Control)					
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 (Control)					
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 (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=1.25, df=1 (P=0.26), I^2=19.75%					



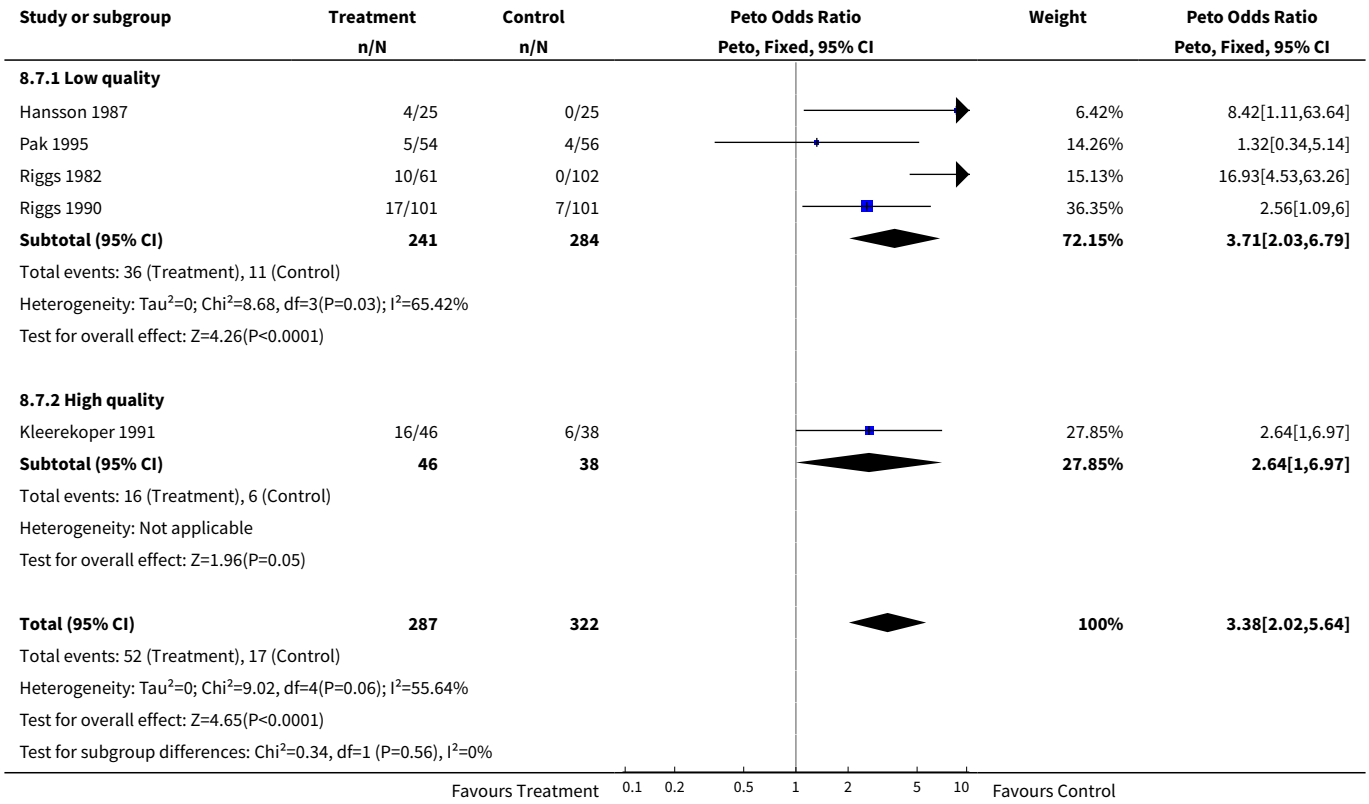
Analysis 8.6. Comparison 8 Sensitivity Quality, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (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)					
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					

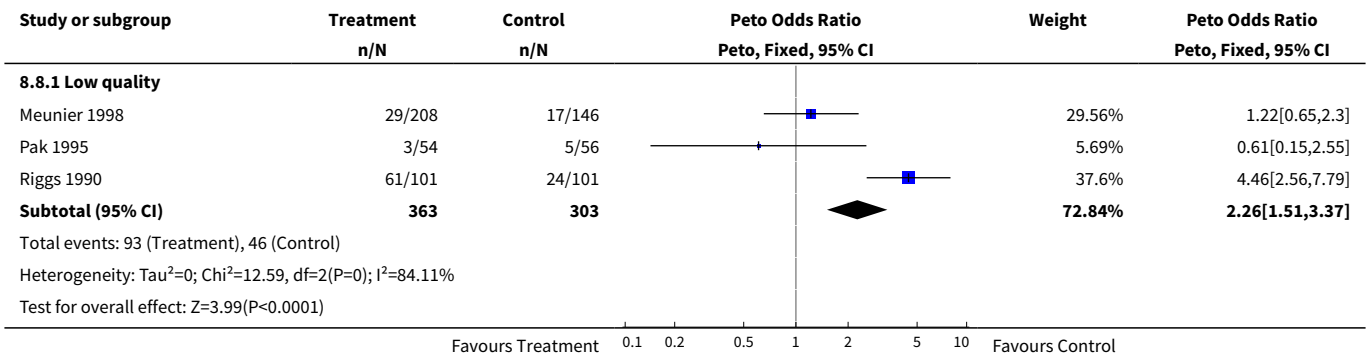


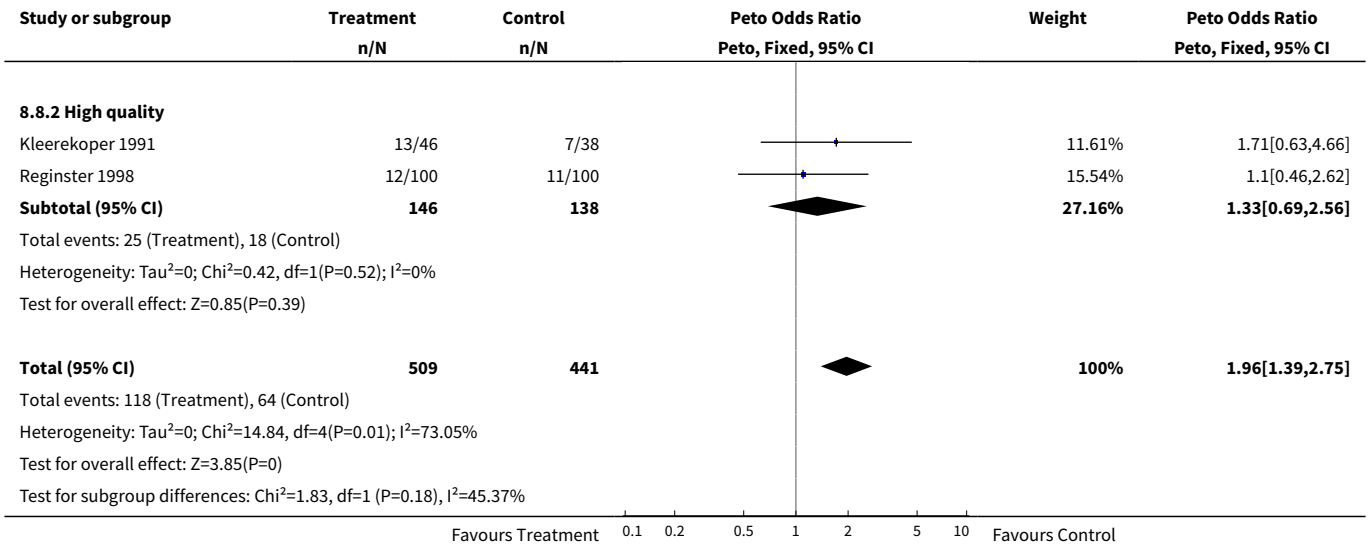


Analysis 8.7. Comparison 8 Sensitivity Quality, Outcome 7 GI minor 4 years.

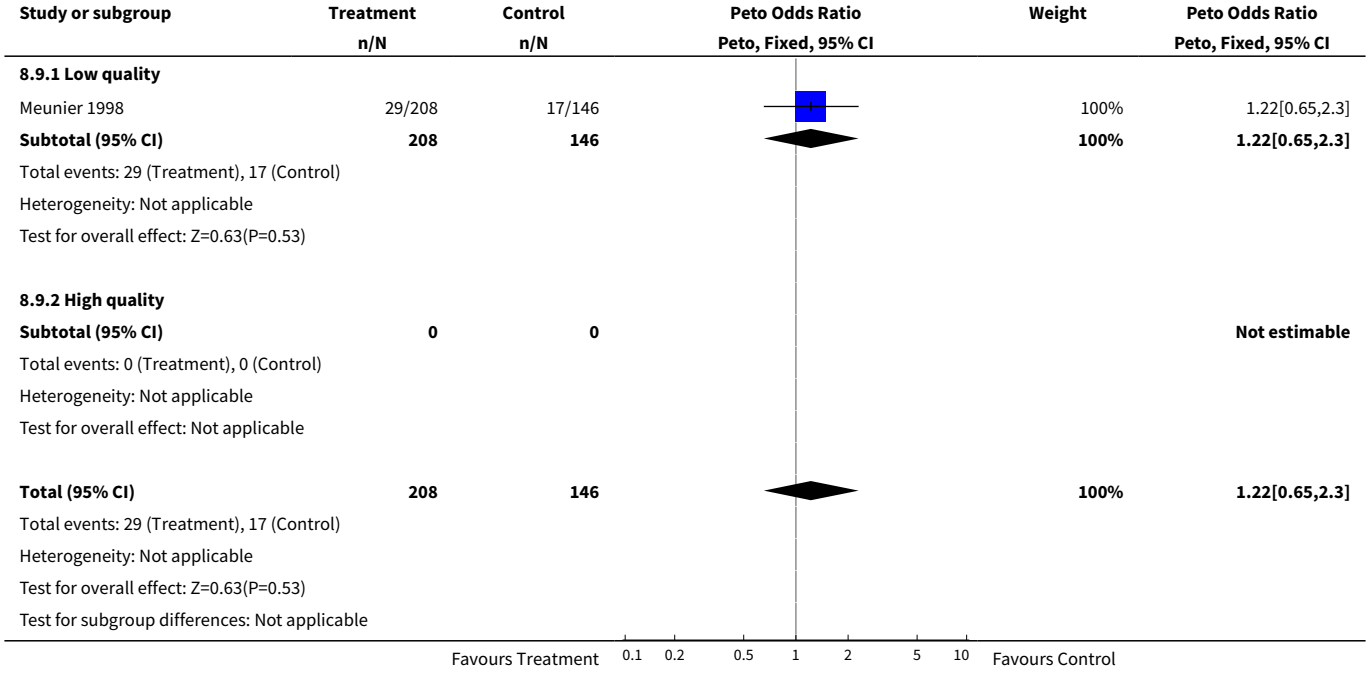


Analysis 8.8. Comparison 8 Sensitivity Quality, Outcome 8 Non vertebral fractures overall.

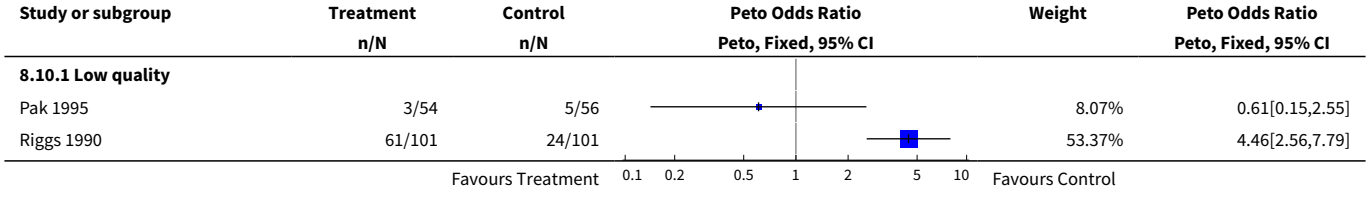


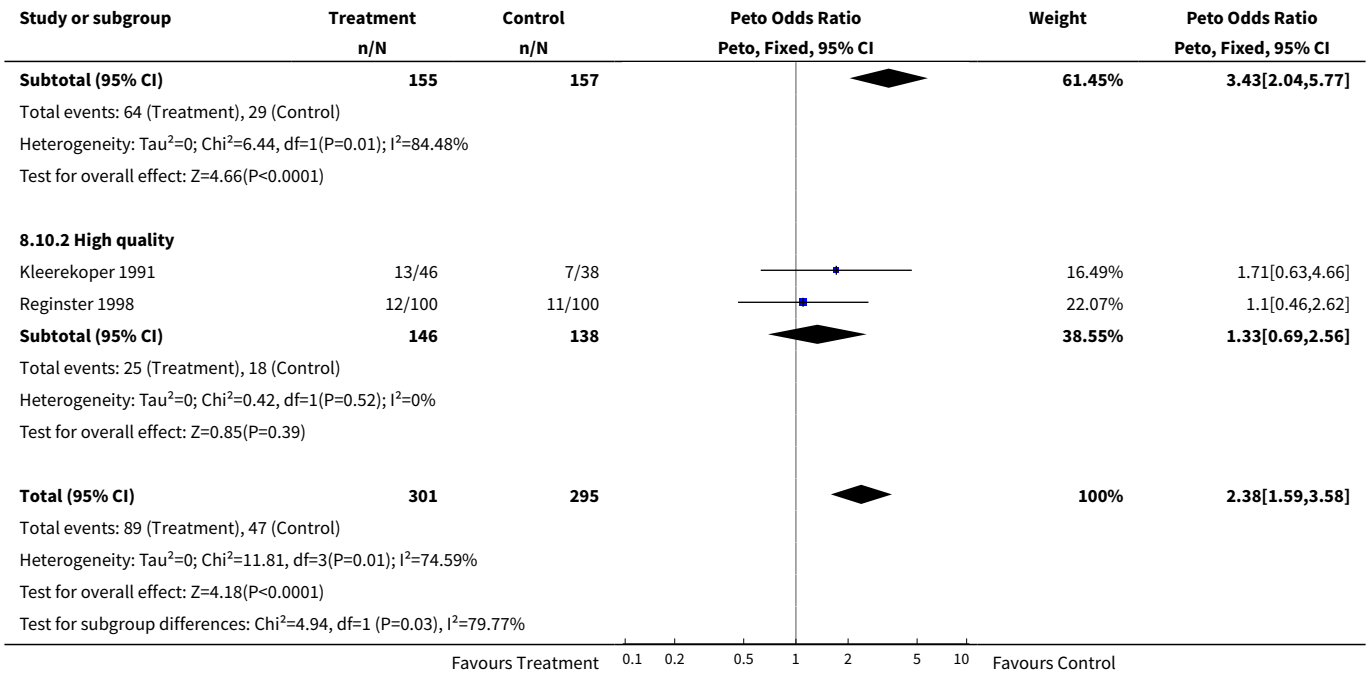


Analysis 8.9. Comparison 8 Sensitivity Quality, Outcome 9 Non vertebral fractures 2 years.

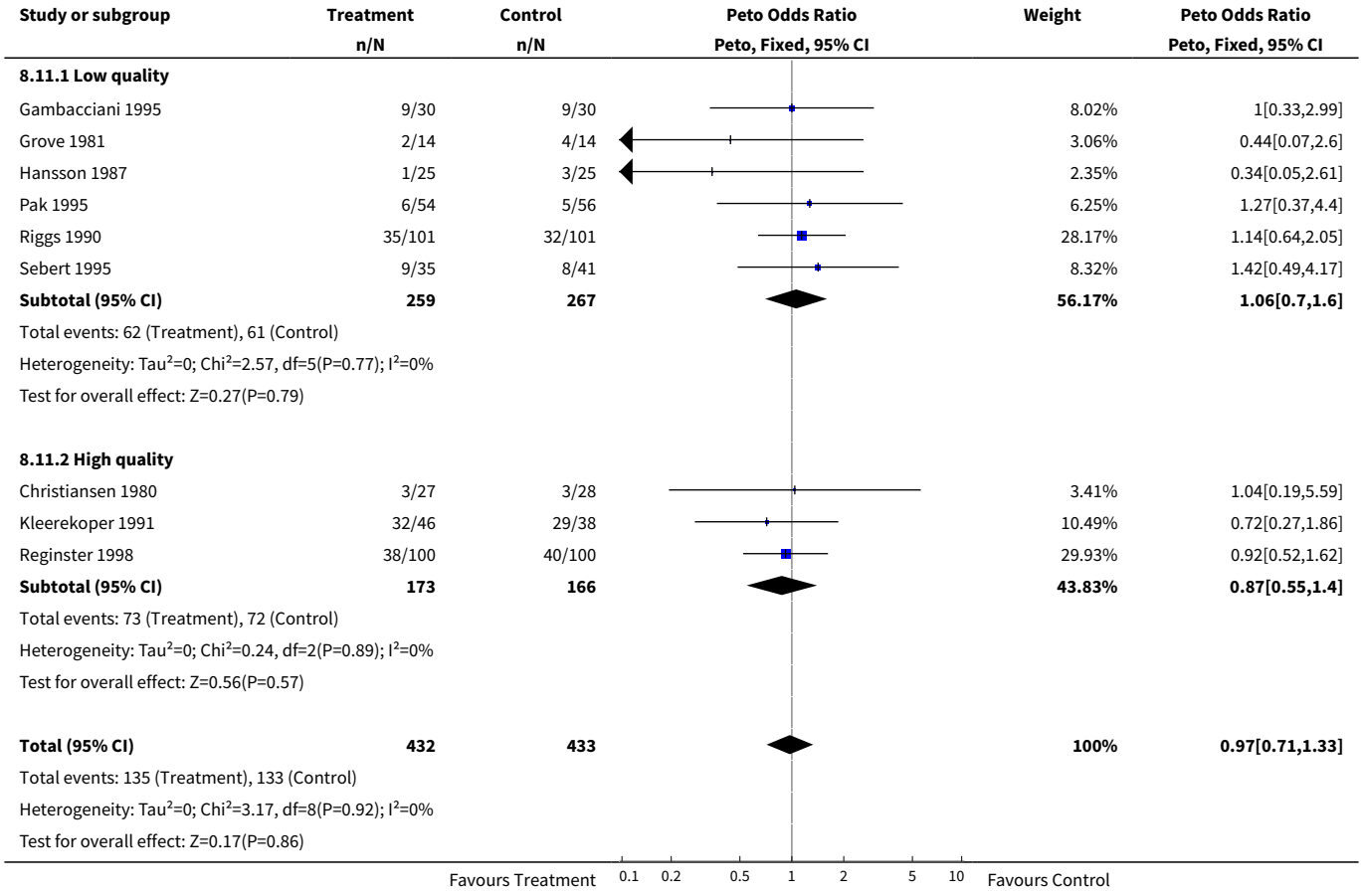


Analysis 8.10. Comparison 8 Sensitivity Quality, Outcome 10 Non vertebral fractures 4 years.





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



Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for subgroup differences: Chi²=0.36, df=1 (P=0.55), I²=0%					

Favours 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.

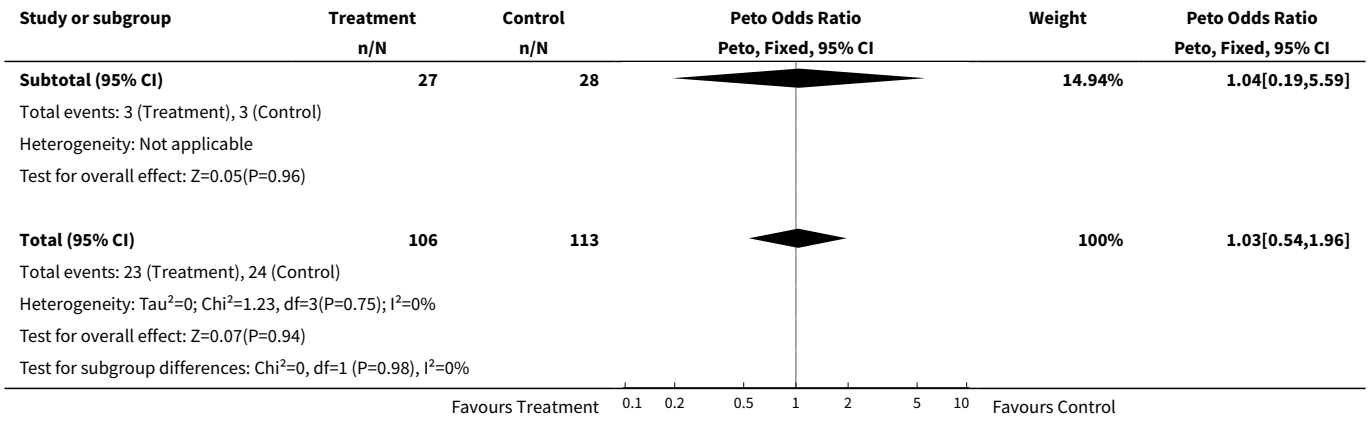
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
8.12.1 Low quality					
Meunier 1998	37/208	7/146		30.59%	3.29[1.73,6.24]
Pak 1995	6/54	8/56		10.07%	0.75[0.25,2.3]
Riggs 1982	14/61	0/102		9.85%	18.27[5.91,56.48]
Riggs 1990	37/101	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)	**469**	**454**		**83.15%**	**4.23[2.87,6.23]**
Total events: 99 (Treatment), 22 (Control)					
Heterogeneity: Tau²=0; Chi²=18.39, df=4(P=0); I²=78.25%					
Test for overall effect: Z=7.27(P<0.0001)					
8.12.2 High quality					
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					
Test for overall effect: Z=1.45(P=0.15)					
Total (95% CI)	**515**	**492**		**100%**	**3.69[2.59,5.26]**
Total events: 122 (Treatment), 35 (Control)					
Heterogeneity: Tau²=0; Chi²=21.16, df=5(P=0); I²=76.38%					
Test for overall effect: Z=7.22(P<0.0001)					
Test for subgroup differences: Chi²=2.77, df=1 (P=0.1), I²=63.94%					

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

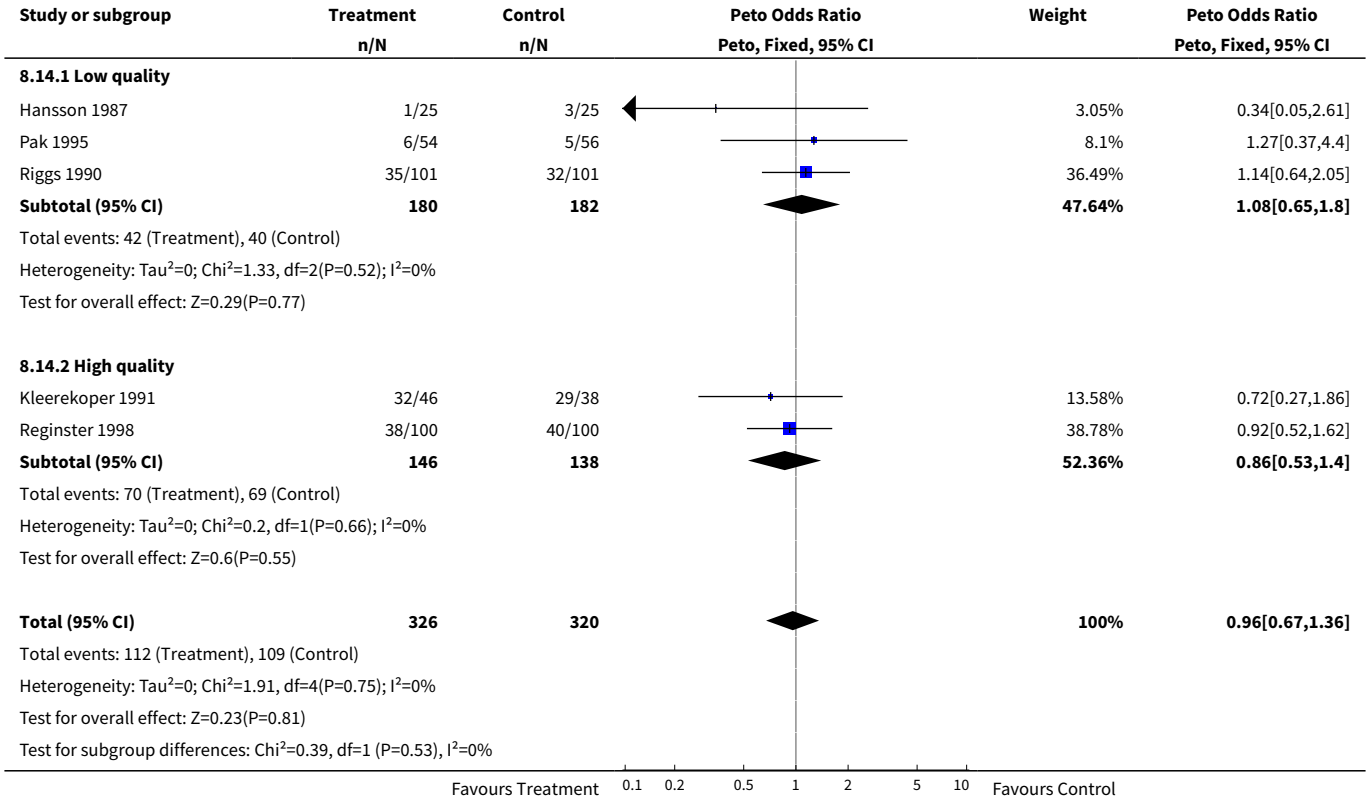
Analysis 8.13. Comparison 8 Sensitivity Quality, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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**		**85.06%**	**1.02[0.51,2.07]**
Total events: 20 (Treatment), 21 (Control)					
Heterogeneity: Tau²=0; Chi²=1.23, df=2(P=0.54); I²=0%					
Test for overall effect: Z=0.06(P=0.95)					
8.13.2 High quality					
Christiansen 1980	3/27	3/28		14.94%	1.04[0.19,5.59]

Favours 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.



Comparison 9. Subgroup men/women

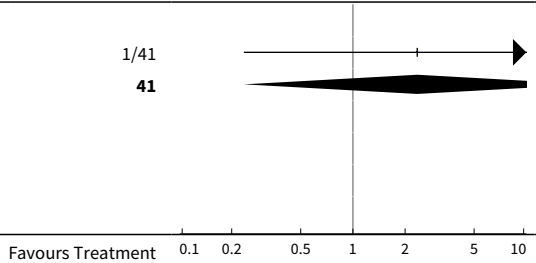
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

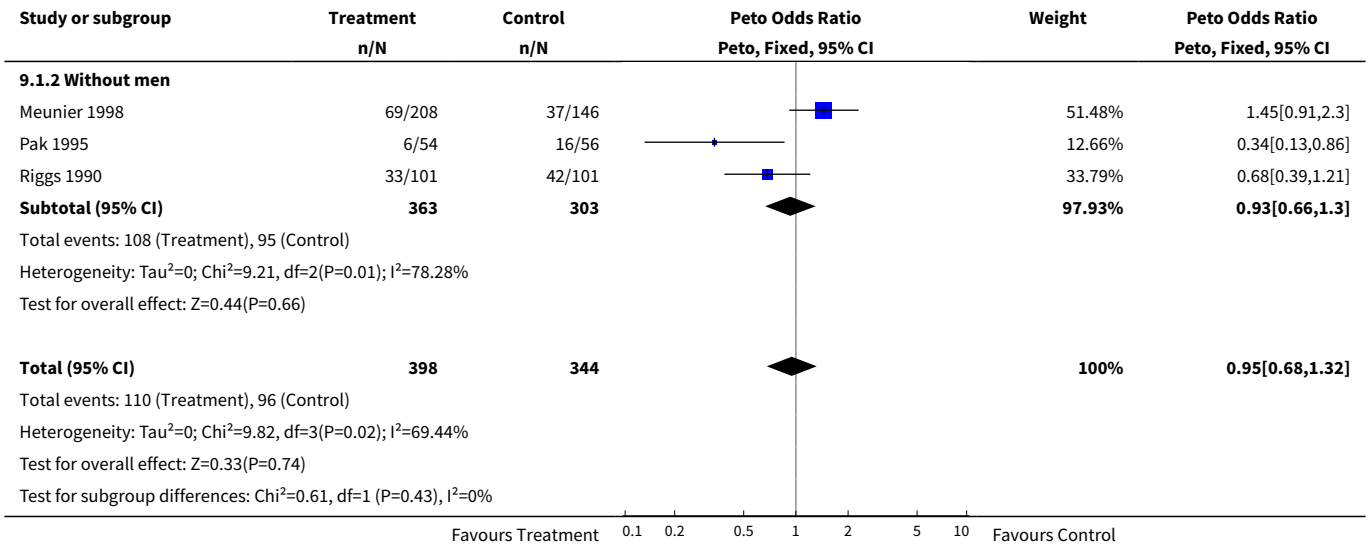
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 With men	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [0.23, 23.42]
1.2 Without men	3	666	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.66, 1.30]
2 No. People with new vertebral fractures 4 years	5	646	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 fractures 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 fractures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

Outcome or subgroup title	No. of studies	No. of participants	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 fractures 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 syndrome	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]

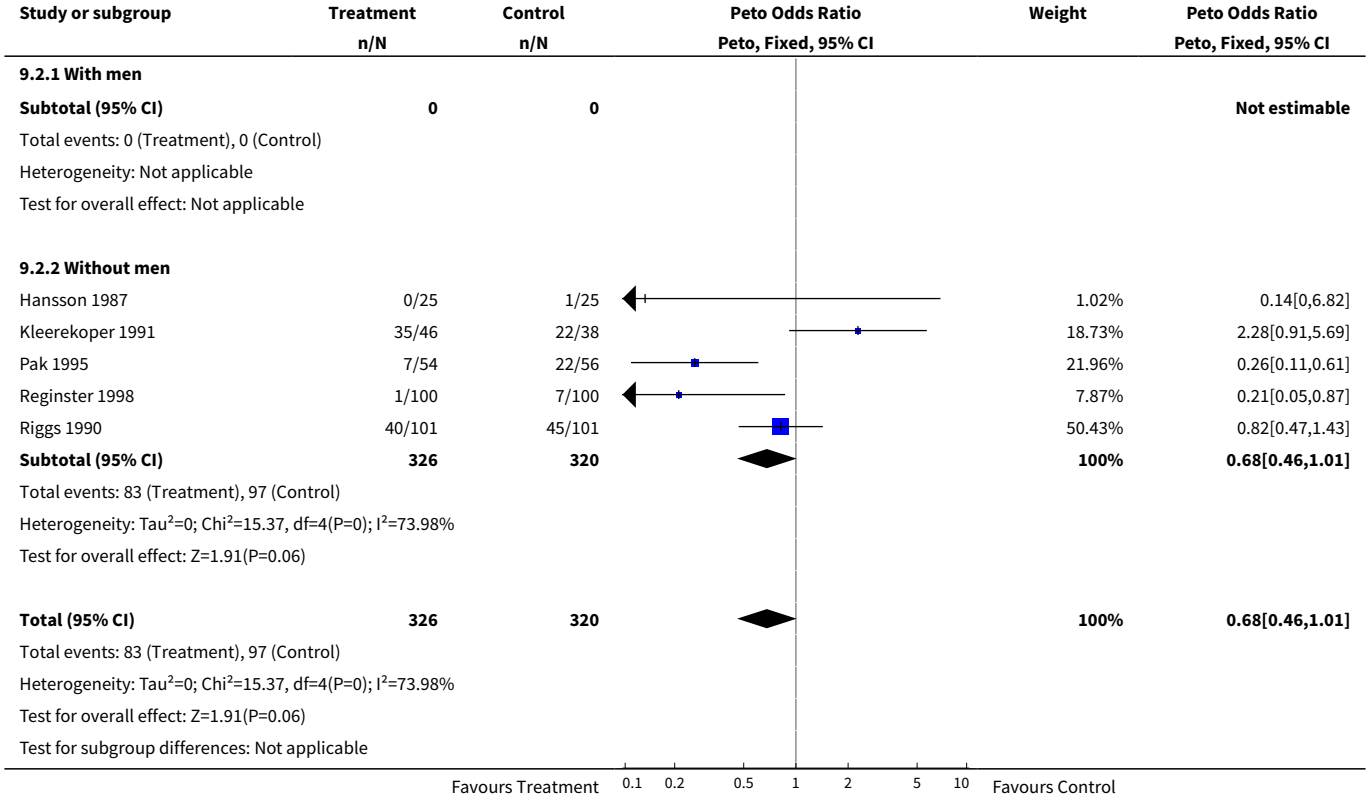
Analysis 9.1. Comparison 9 Subgroup men/women, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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)					



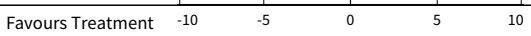


Analysis 9.2. Comparison 9 Subgroup men/women, Outcome 2 No. People with new vertebral fractures 4 years.



Analysis 9.3. Comparison 9 Subgroup men/women, Outcome 3 Lumbar BMD % 2 years from baseline.

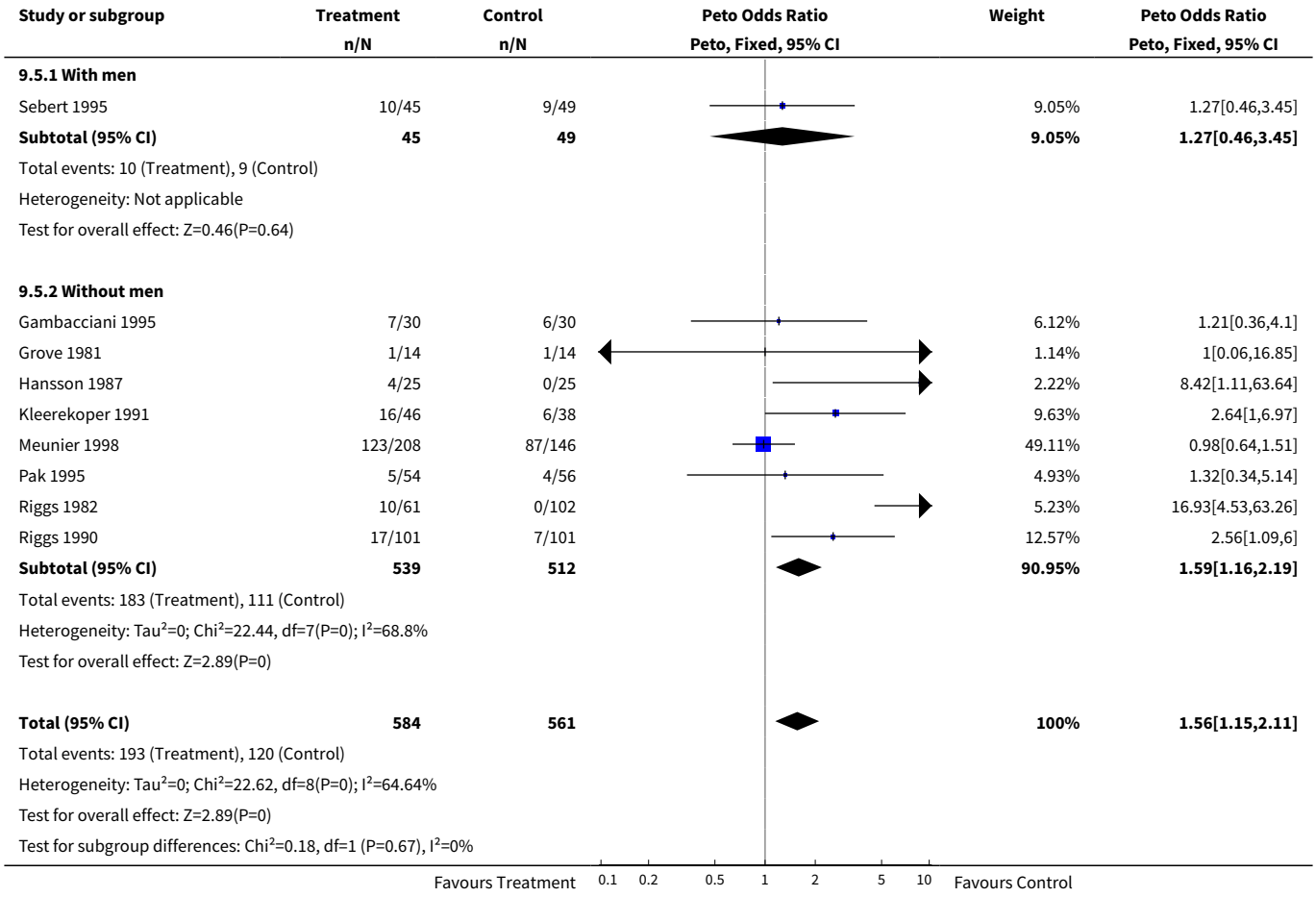
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.3.1 With men							
Sebert 1995	26	114.3 (13)	33	103.3 (10.7)		2.2%	11.06[4.88,17.24]
Subtotal ***	**26**		**33**			**2.2%**	**11.06[4.88,17.24]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=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: Tau²=0; Chi²=92.5, df=5(P<0.0001); I²=94.59%							
Test for overall effect: Z=20.52(P<0.0001)							
Total ***	**466**		**536**			**100%**	**9.73[8.82,10.65]**
Heterogeneity: Tau²=0; Chi²=92.68, df=6(P<0.0001); I²=93.53%							
Test for overall effect: Z=20.82(P<0.0001)							
Test for subgroup differences: Chi²=0.18, df=1 (P=0.67), I²=0%							



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

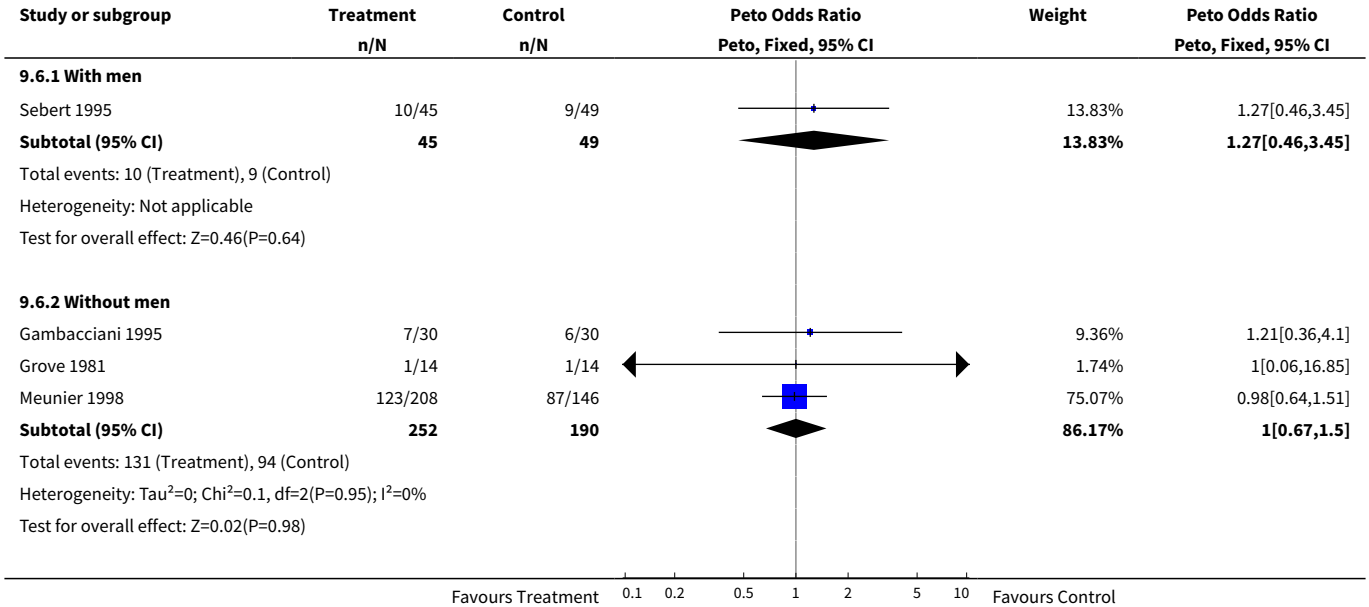
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.4.1 With men							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
9.4.2 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: Tau²=0; Chi²=180.91, df=2(P<0.0001); I²=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau²=0; Chi²=180.91, df=2(P<0.0001); I²=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Not applicable							

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

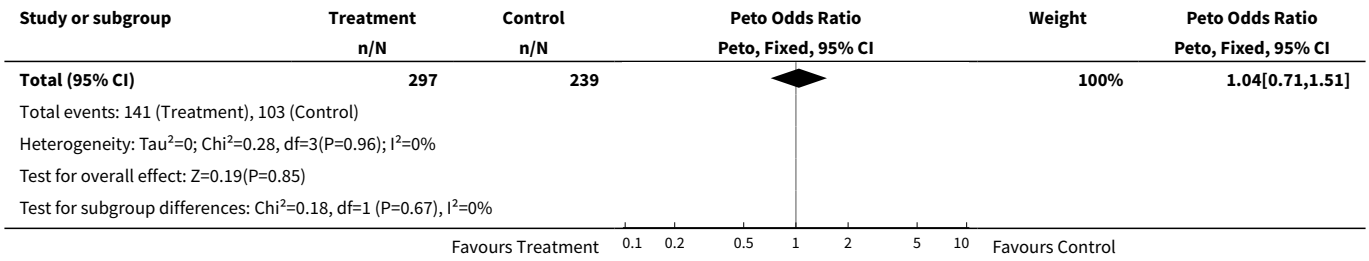


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
9.5.1 With men					
Sebert 1995	10/45	9/49		9.05%	1.27[0.46,3.45]
Subtotal (95% CI)	**45**	**49**		**9.05%**	**1.27[0.46,3.45]**
Total events: 10 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					
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), I^2=0%					

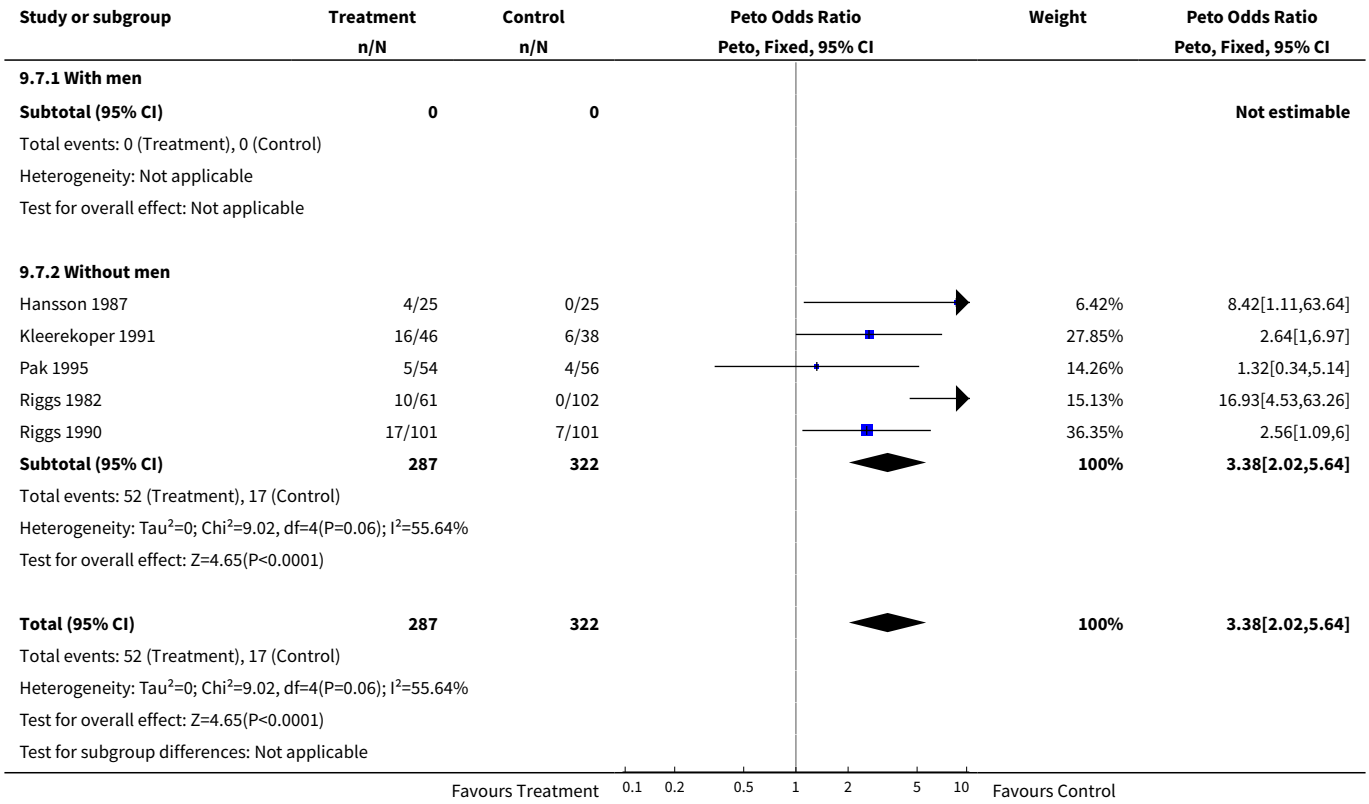
Analysis 9.6. Comparison 9 Subgroup men/women, Outcome 6 GI minor 2 years.



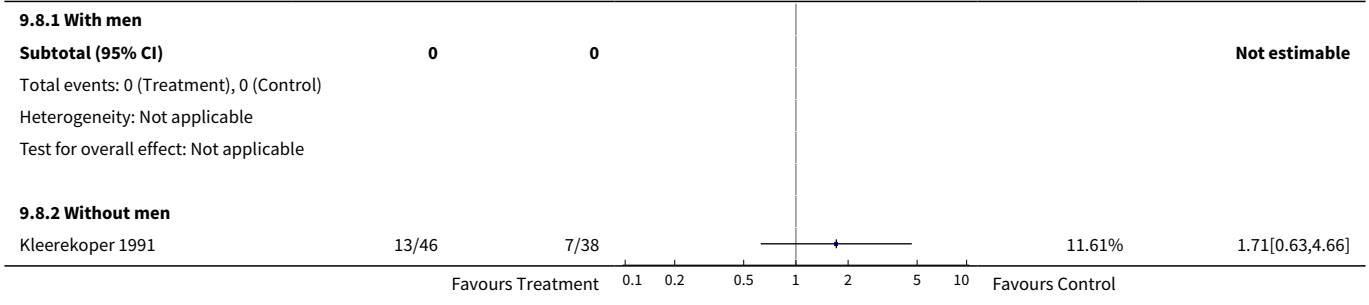
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
9.6.1 With men					
Sebert 1995	10/45	9/49		13.83%	1.27[0.46,3.45]
Subtotal (95% CI)	**45**	**49**		**13.83%**	**1.27[0.46,3.45]**
Total events: 10 (Treatment), 9 (Control)					
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		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**		**86.17%**	**1[0.67,1.5]**
Total events: 131 (Treatment), 94 (Control)					
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)					

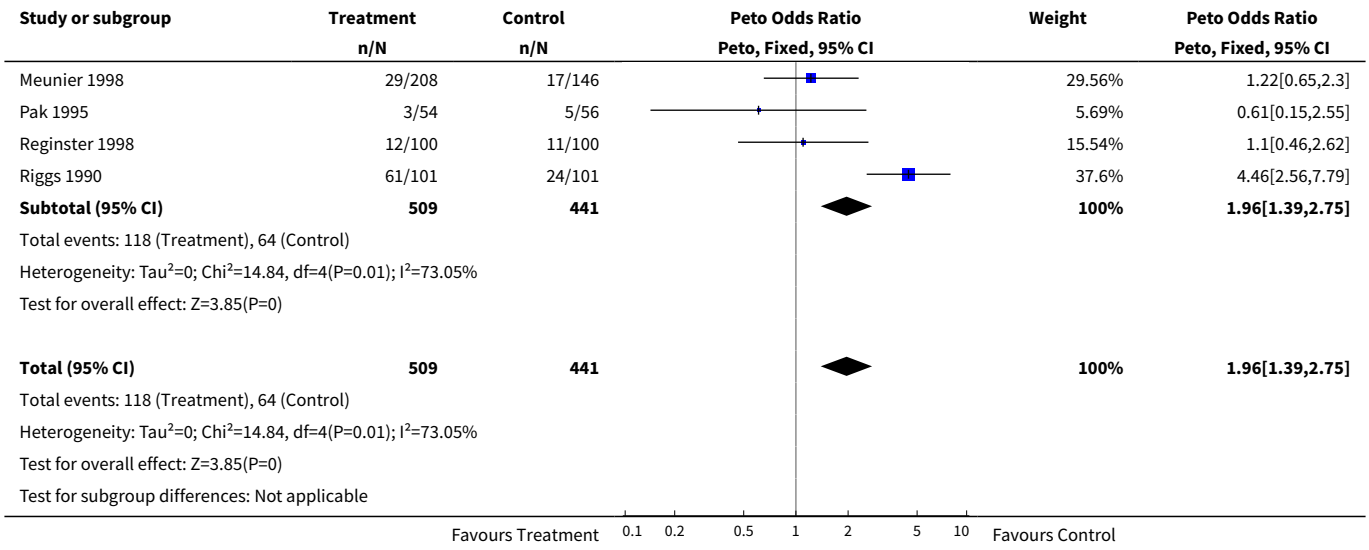


Analysis 9.7. Comparison 9 Subgroup men/women, Outcome 7 GI minor 4 years.

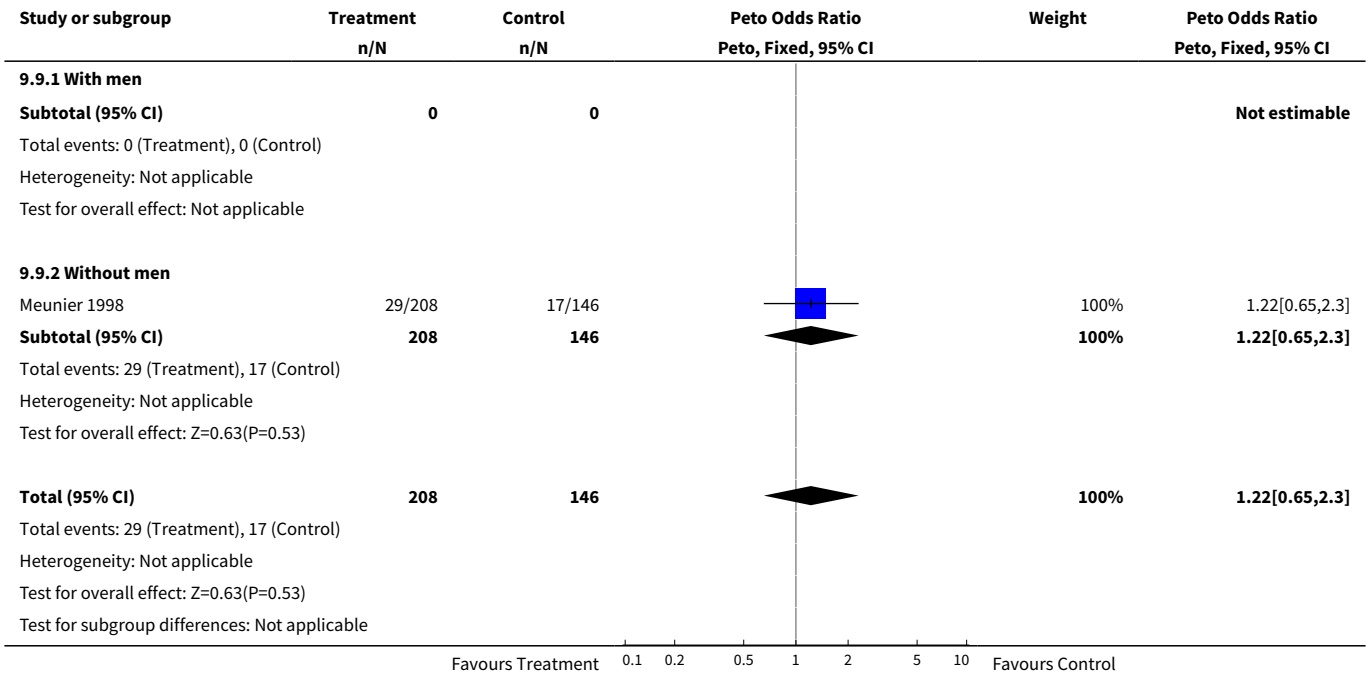


Analysis 9.8. Comparison 9 Subgroup men/women, Outcome 8 Non vertebral fractures overall.

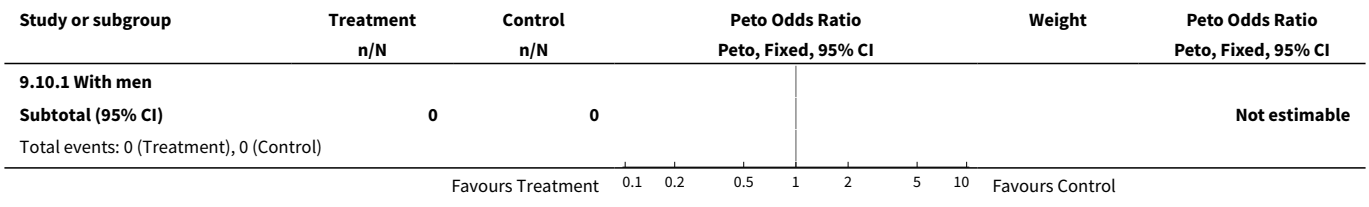


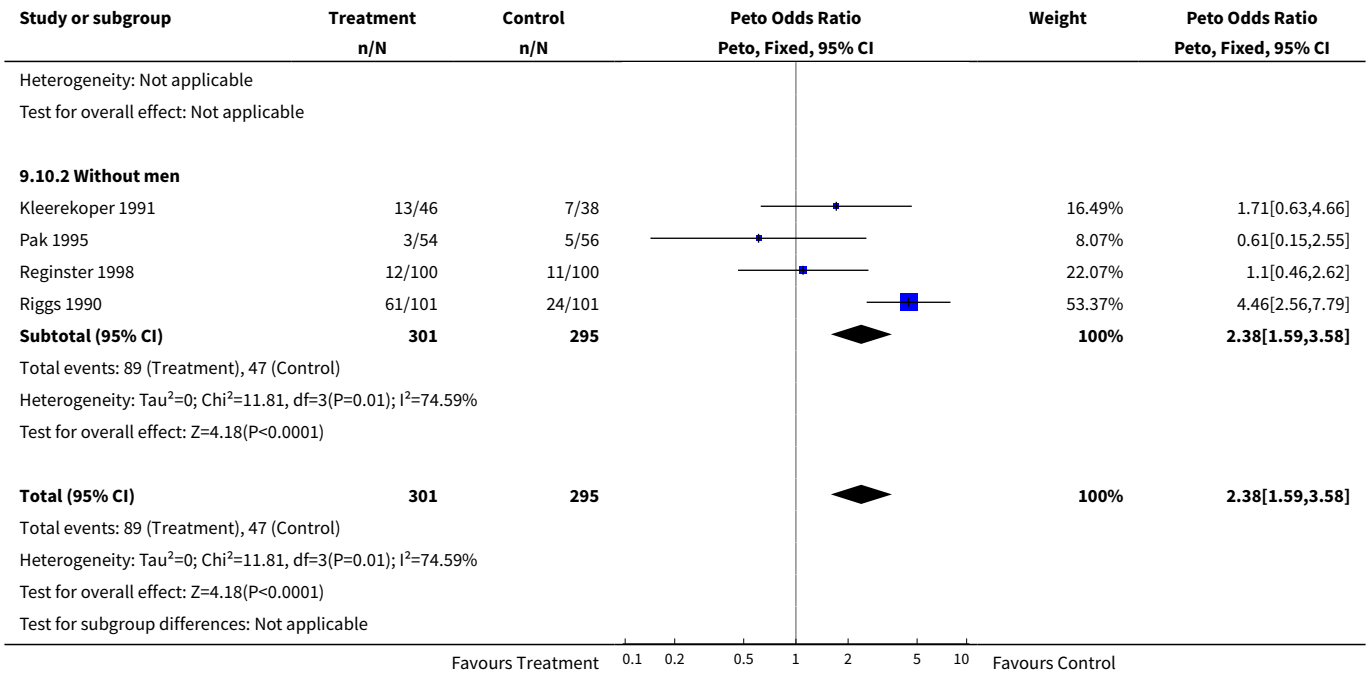


Analysis 9.9. Comparison 9 Subgroup men/women, Outcome 9 Non vertebral fractures 2 years.

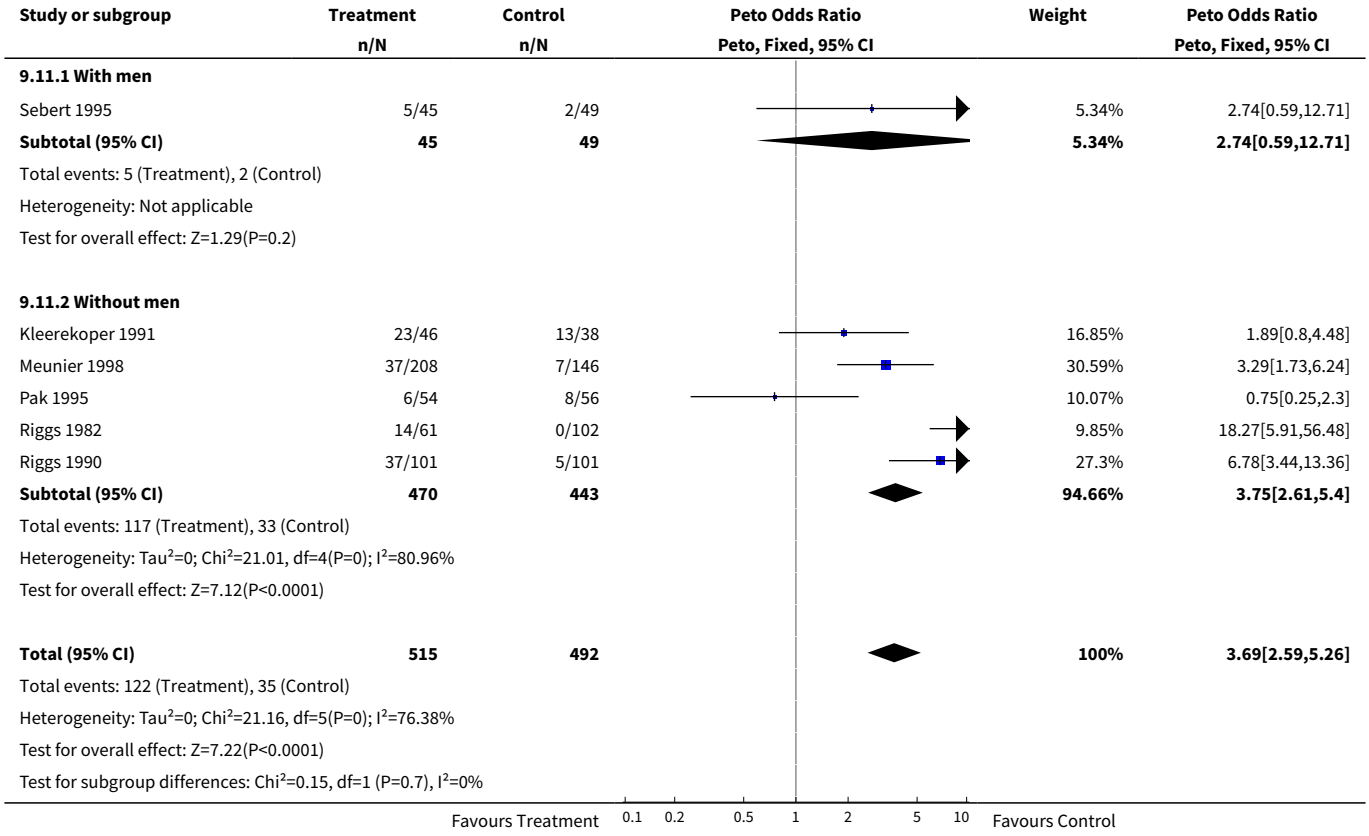


Analysis 9.10. Comparison 9 Subgroup men/women, Outcome 10 Non vertebral fractures 4 years.



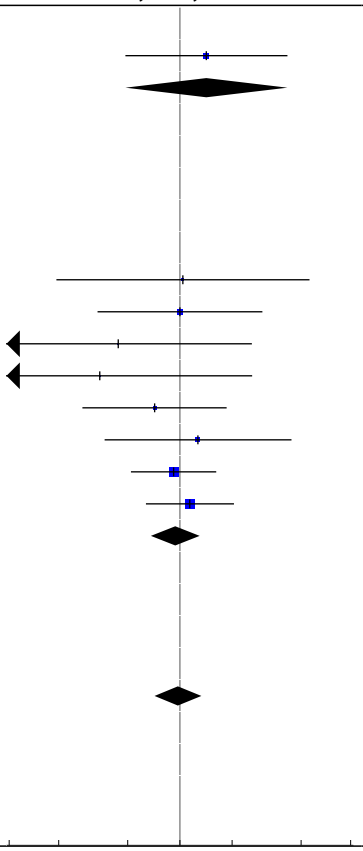


Analysis 9.11. Comparison 9 Subgroup men/women, Outcome 11 Lower limb pain syndrome.



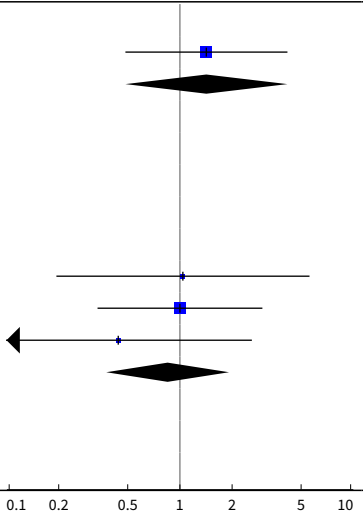
Analysis 9.12. Comparison 9 Subgroup men/women, Outcome 12 Withdrawals and dropouts overall.

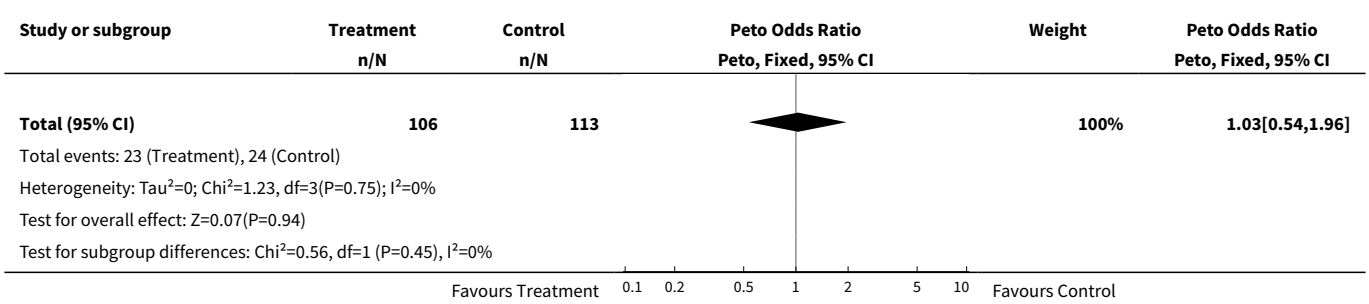
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
9.12.1 With men					
Sebert 1995	9/35	8/41		8.32%	1.42[0.49,4.17]
Subtotal (95% CI)	**35**	**41**		**8.32%**	**1.42[0.49,4.17]**
Total events: 9 (Treatment), 8 (Control)					
Heterogeneity: 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 (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 (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=0.52, df=1 (P=0.47), I^2=0%					



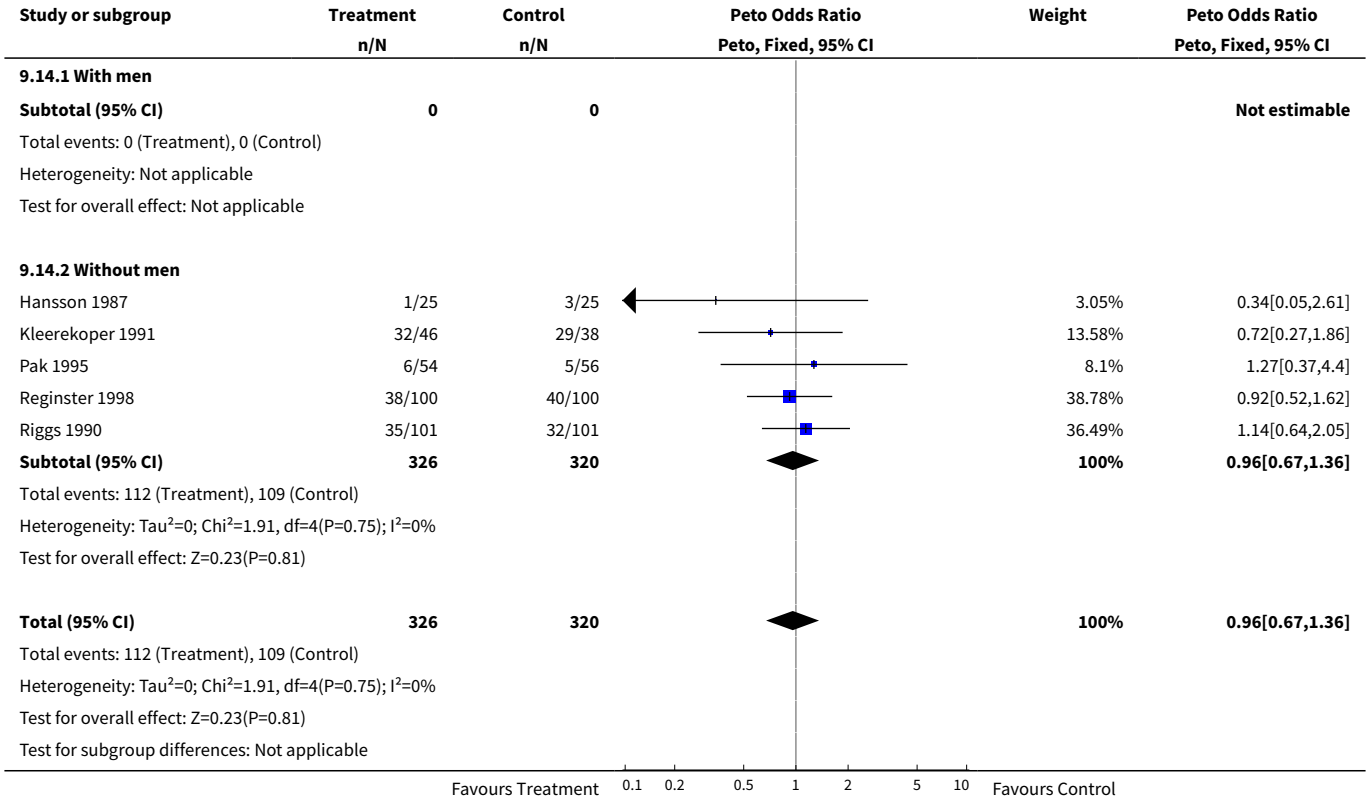
Analysis 9.13. Comparison 9 Subgroup men/women, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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)					
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 (Control)					
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)					





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



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

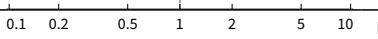
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 With vit D = EC	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.91, 2.30]
1.2 Without vit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

Outcome or subgroup title	No. of studies	No. of participants	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 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]

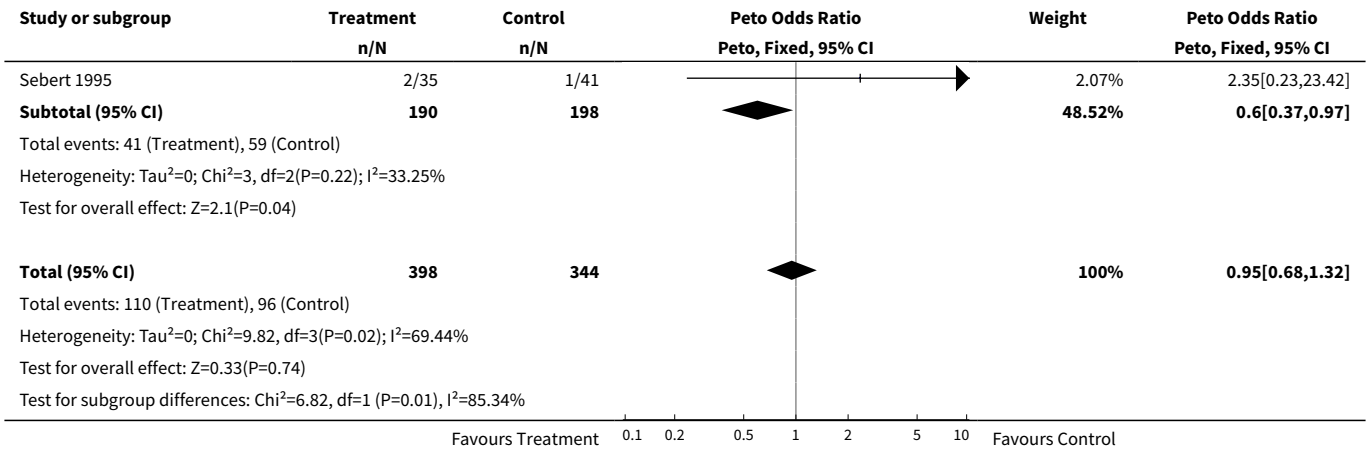
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Non vertebral fractures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 With vit D = EC	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Without vit D = non EC	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
11 Lower limb pain syndrome	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.

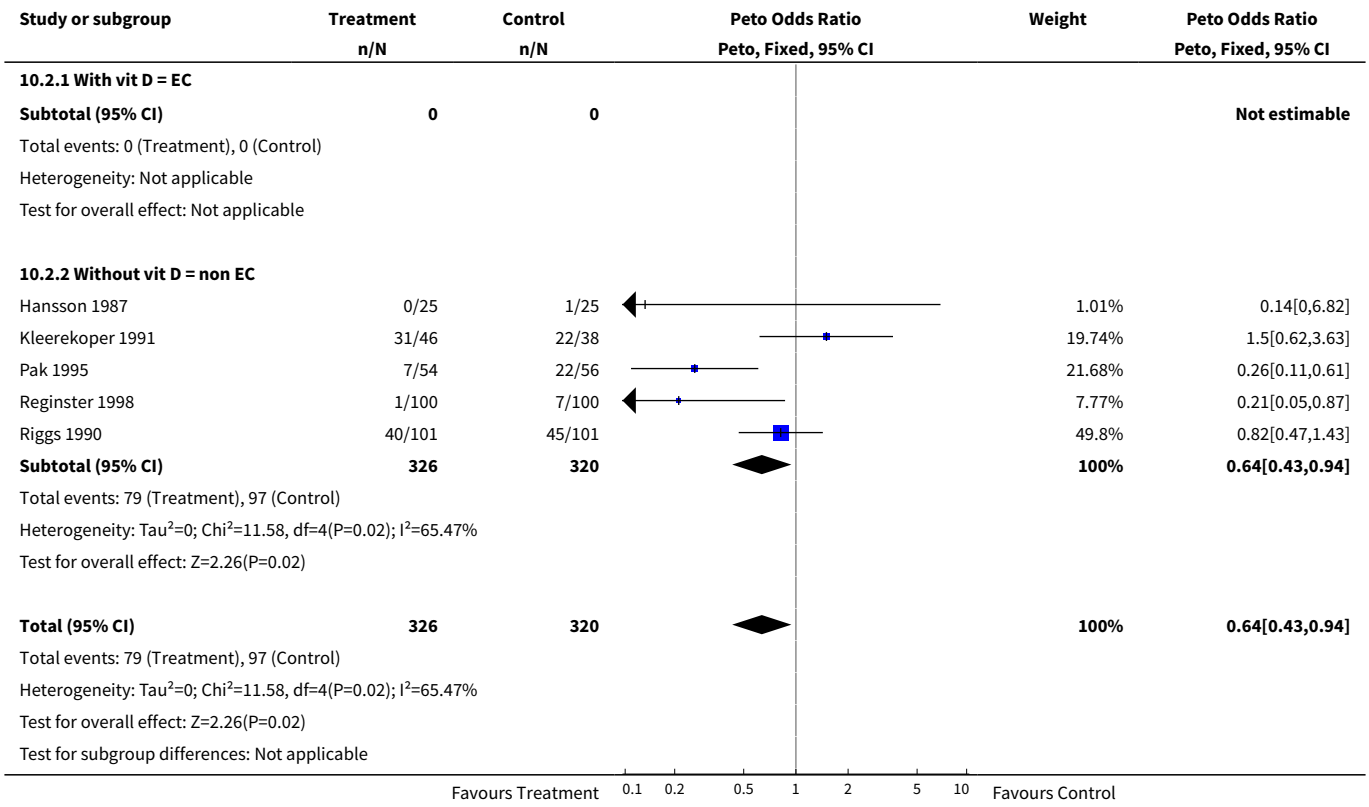
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
10.1.1 With vit D = EC					
Meunier 1998	69/208	37/146		51.48%	1.45[0.91,2.3]
Subtotal (95% CI)	**208**	**146**		**51.48%**	**1.45[0.91,2.3]**
Total events: 69 (Treatment), 37 (Control)					
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]



Favours Treatment — Favours Control

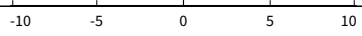


Analysis 10.2. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 2 No. People with new vertebral fractures 4 years.



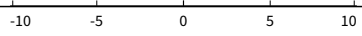
Analysis 10.3. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 3 Lumbar BMD % 2 years from baseline.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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)							
10.3.2 Without vit D = non EC							
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, df=5(P<0.0001); I^2=94.59%							
Test for overall effect: Z=20.59(P<0.0001)							
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<0.0001)							
Test for subgroup differences: Chi^2=0.25, df=1 (P=0.62), I^2=0%							

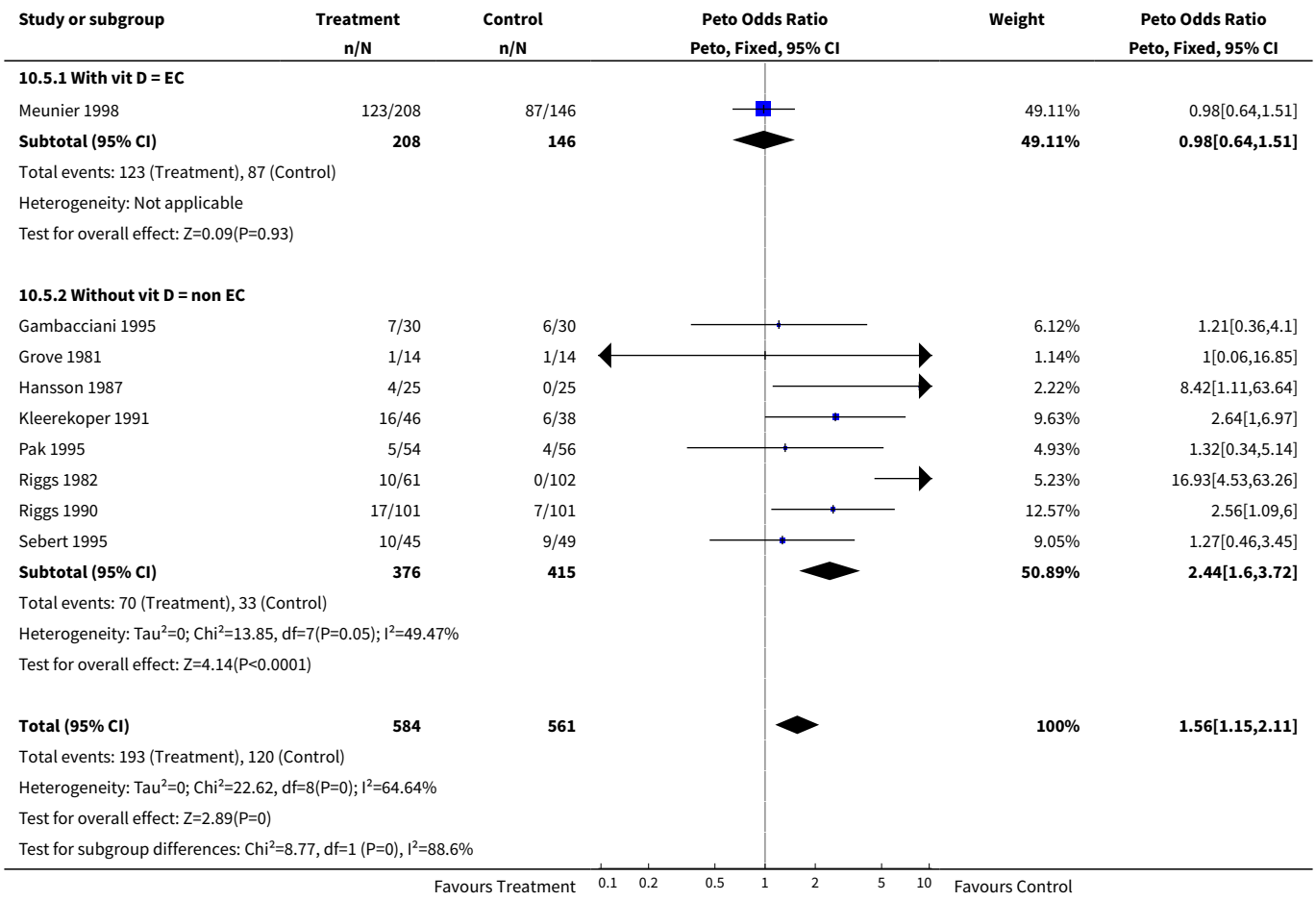


Analysis 10.4. Comparison 10 Subgroup Vit D/ no vit D = EC/ Non EC, Outcome 4 Lumbar BMD % 4 years from baseline.

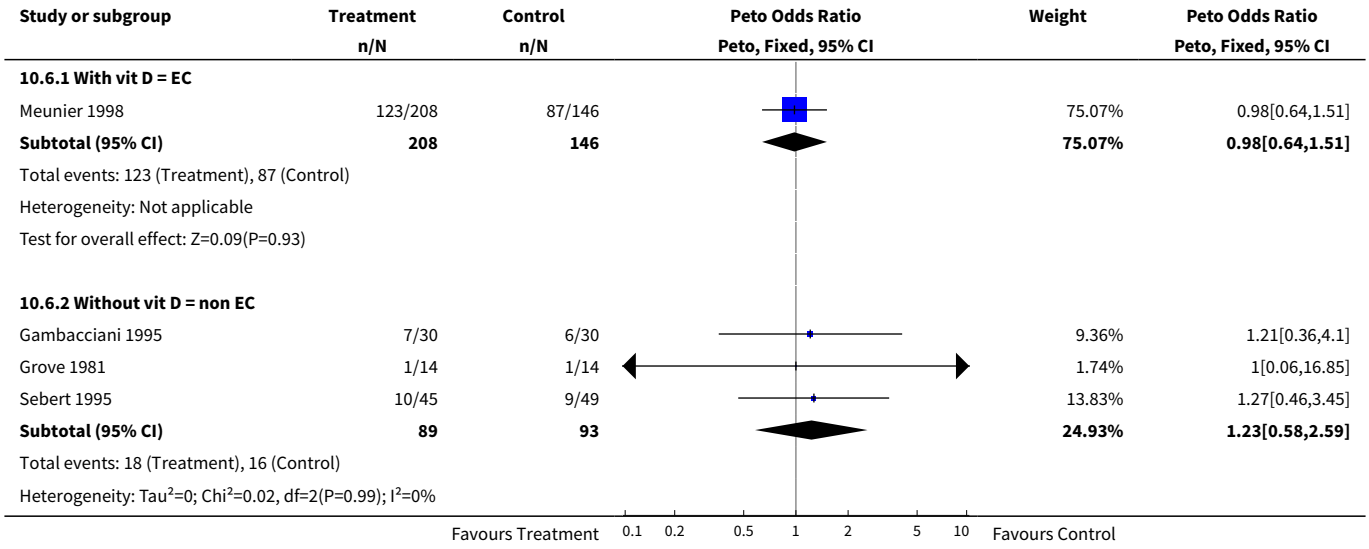
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
10.4.1 With vit D = EC							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
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, df=2(P<0.0001); I^2=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau^2=0; Chi^2=180.91, df=2(P<0.0001); I^2=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Not applicable							

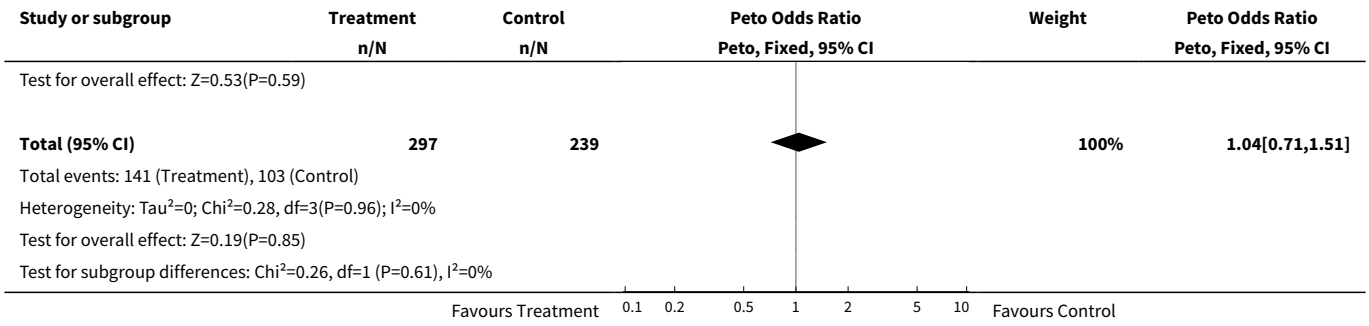


Analysis 10.5. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 5 GI minor overall.

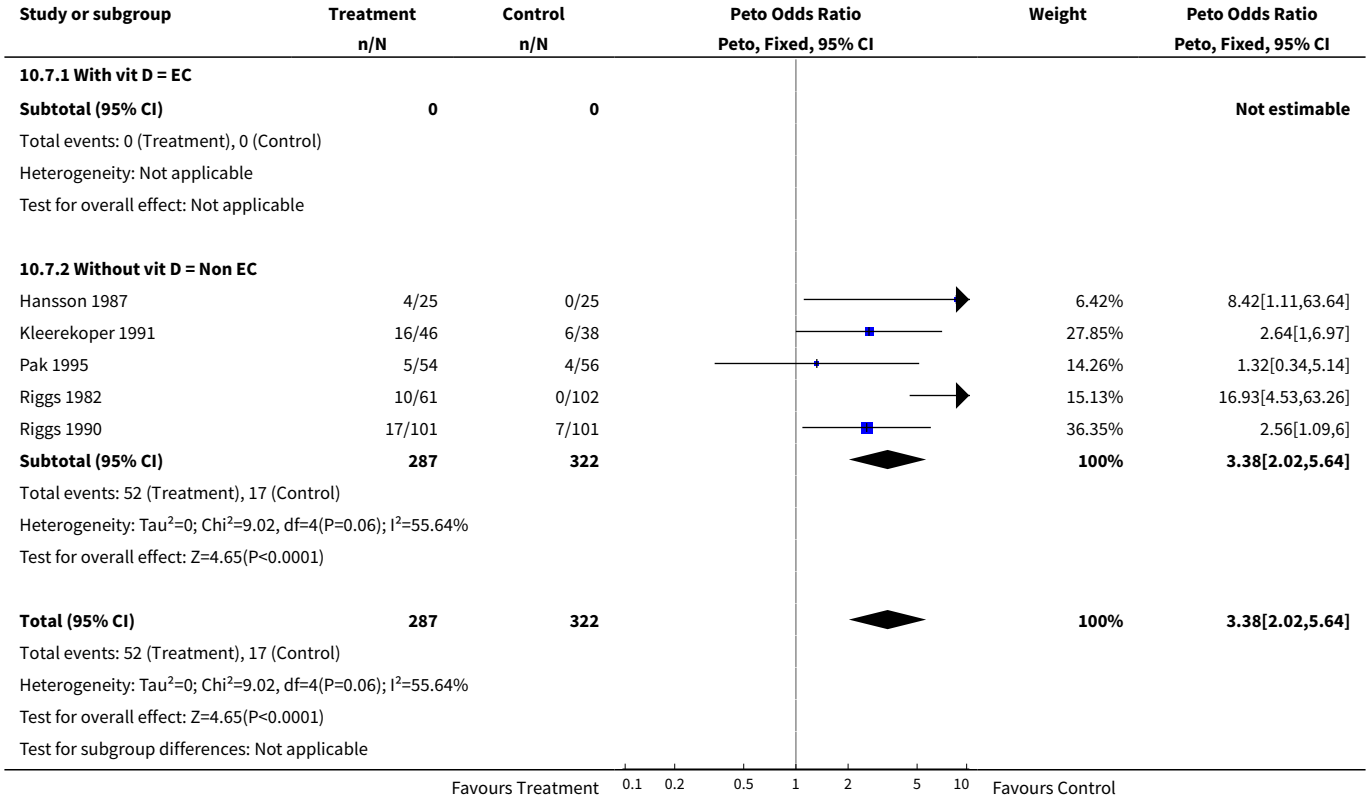


Analysis 10.6. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 6 GI minor 2 years.

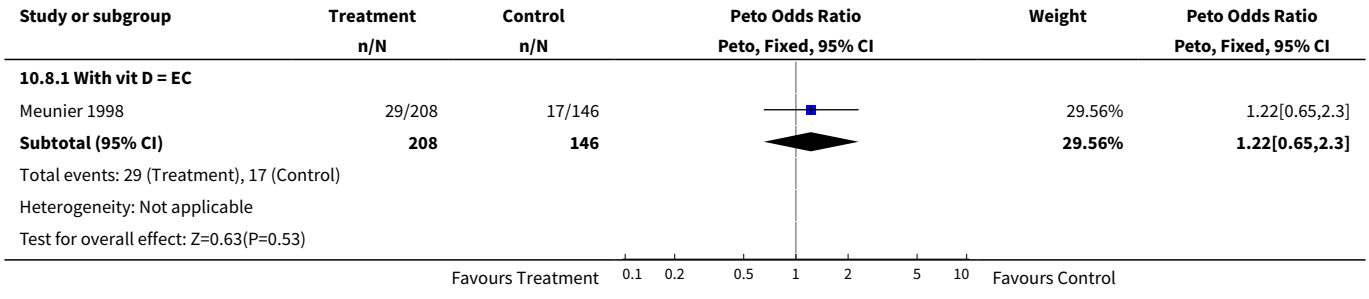


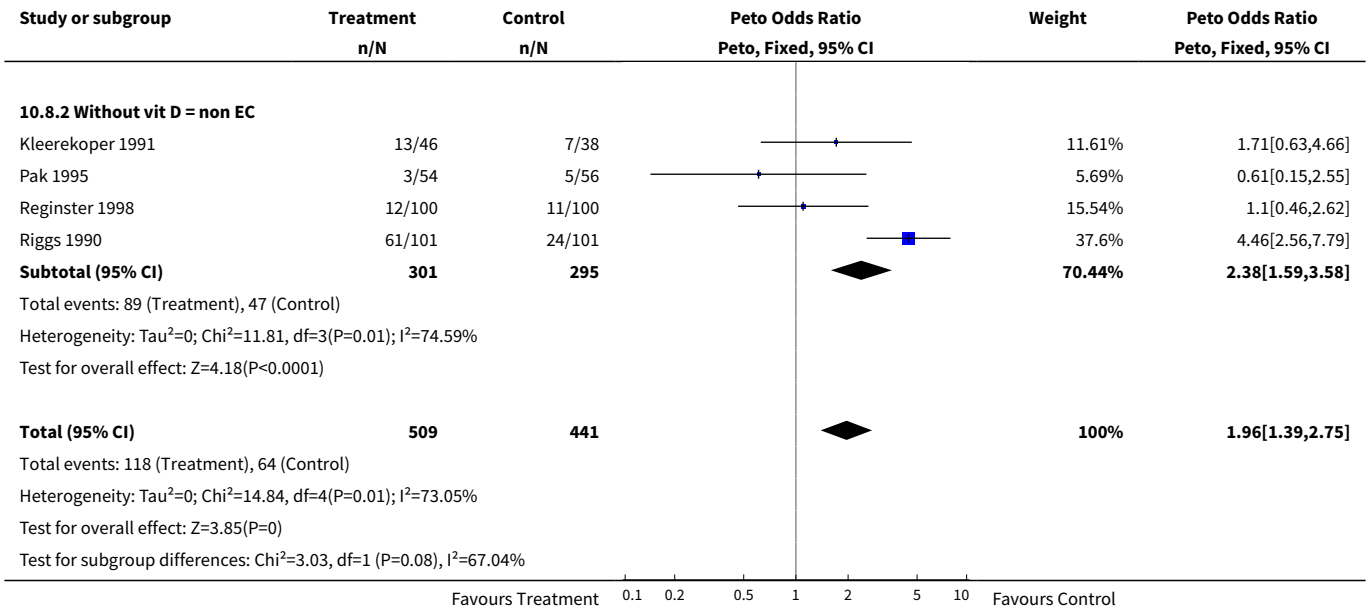


Analysis 10.7. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 7 GI minor 4 years.

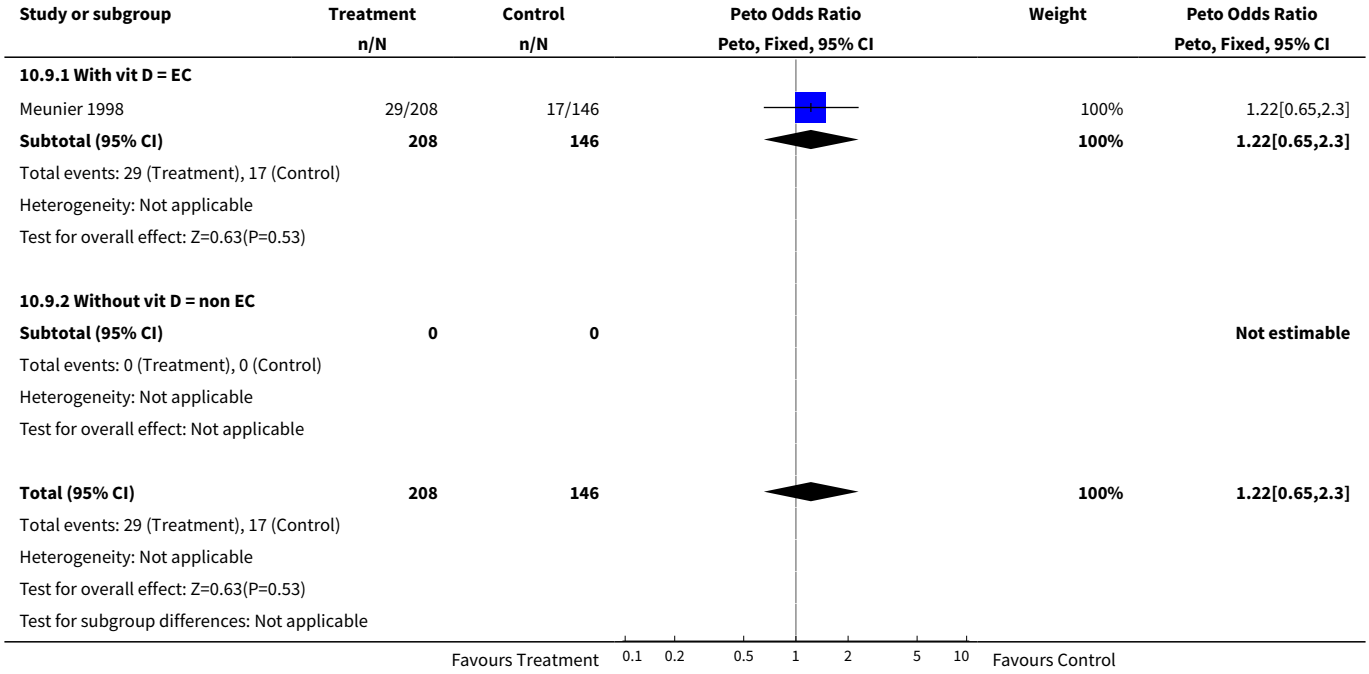


Analysis 10.8. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 8 Non vertebral fractures overall.

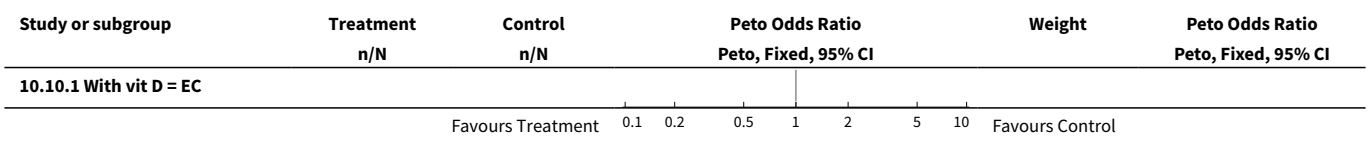


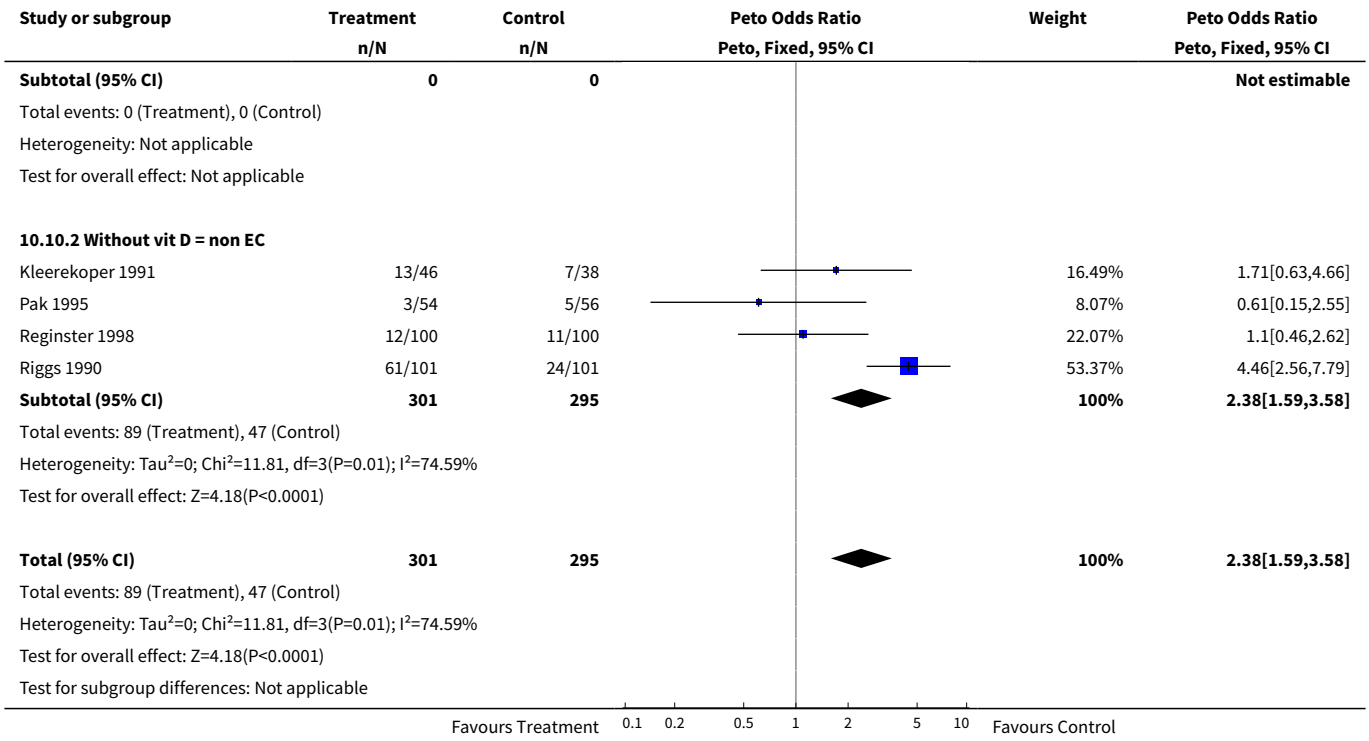


Analysis 10.9. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 9 Non vertebral fractures 2 years.

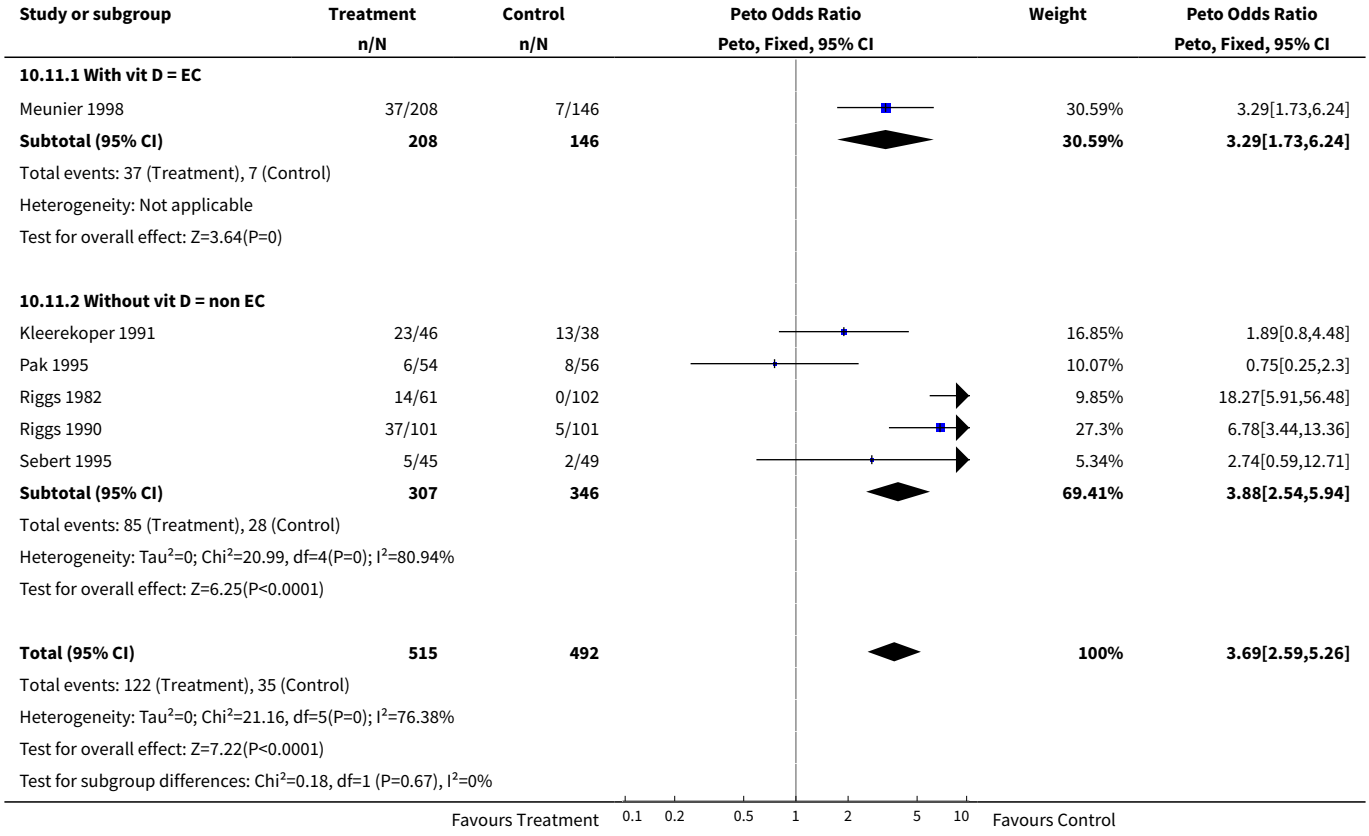


Analysis 10.10. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 10 Non vertebral fractures 4 years.





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

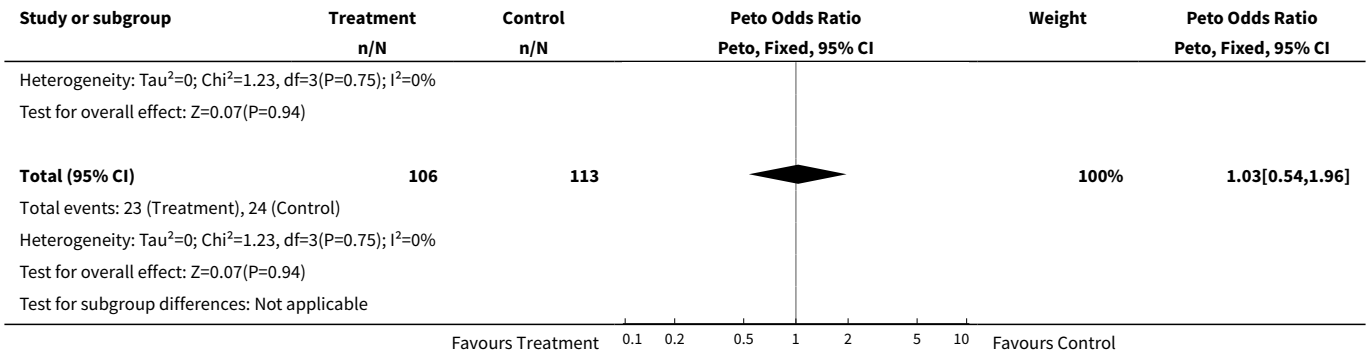


Analysis 10.12. Comparison 10 Subgroup Vit D/ no vit D = EC/Non EC, Outcome 12 Withdrawals and dropouts overall.

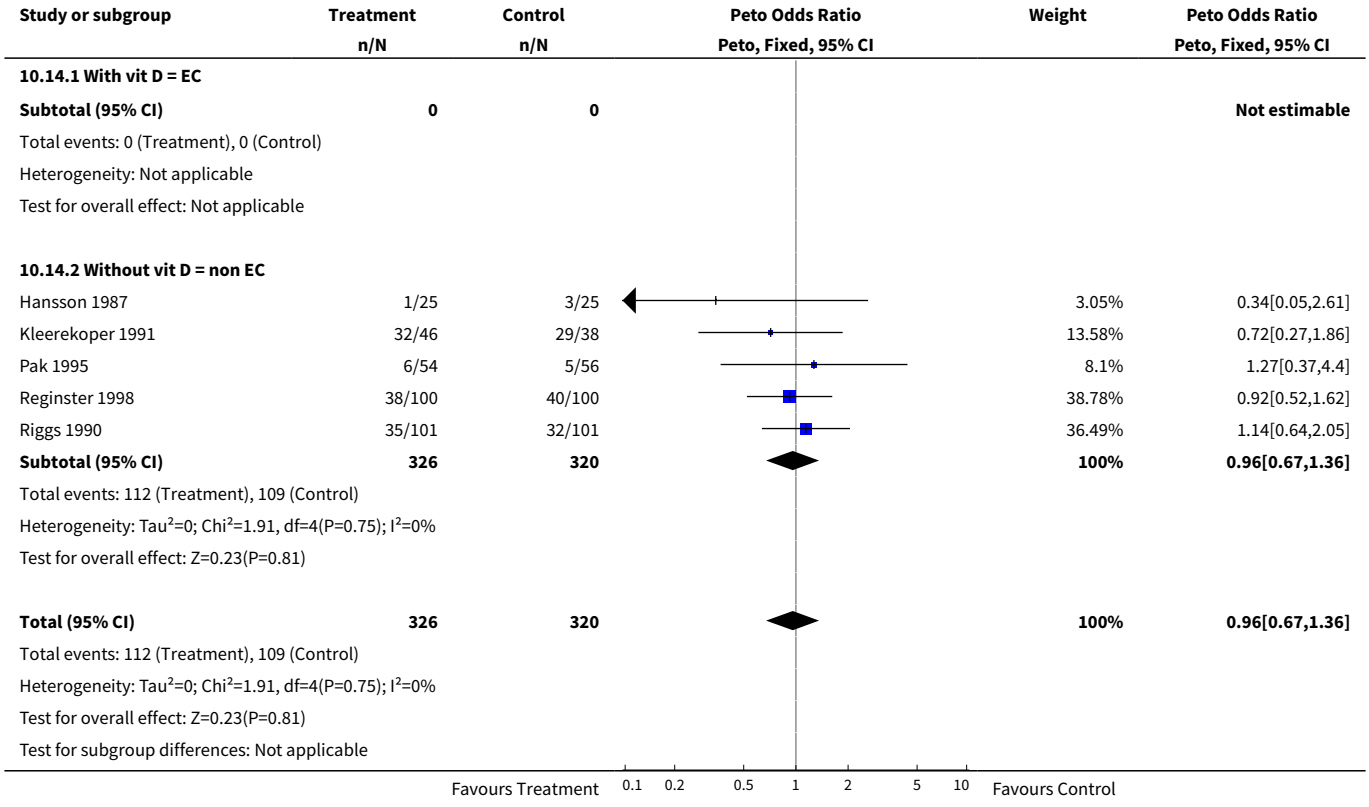
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
10.12.1 With vit D = EC					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: 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 (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)					
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)					
Test for subgroup differences: Not applicable					

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 n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 (Control)					



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



Comparison 11. Subgroup HRT/non HRT

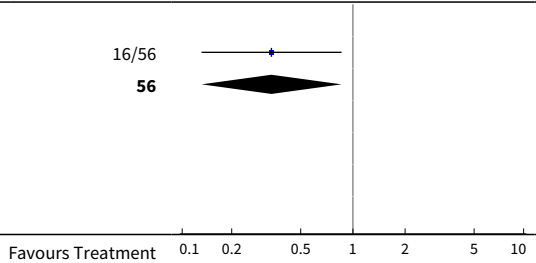
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]

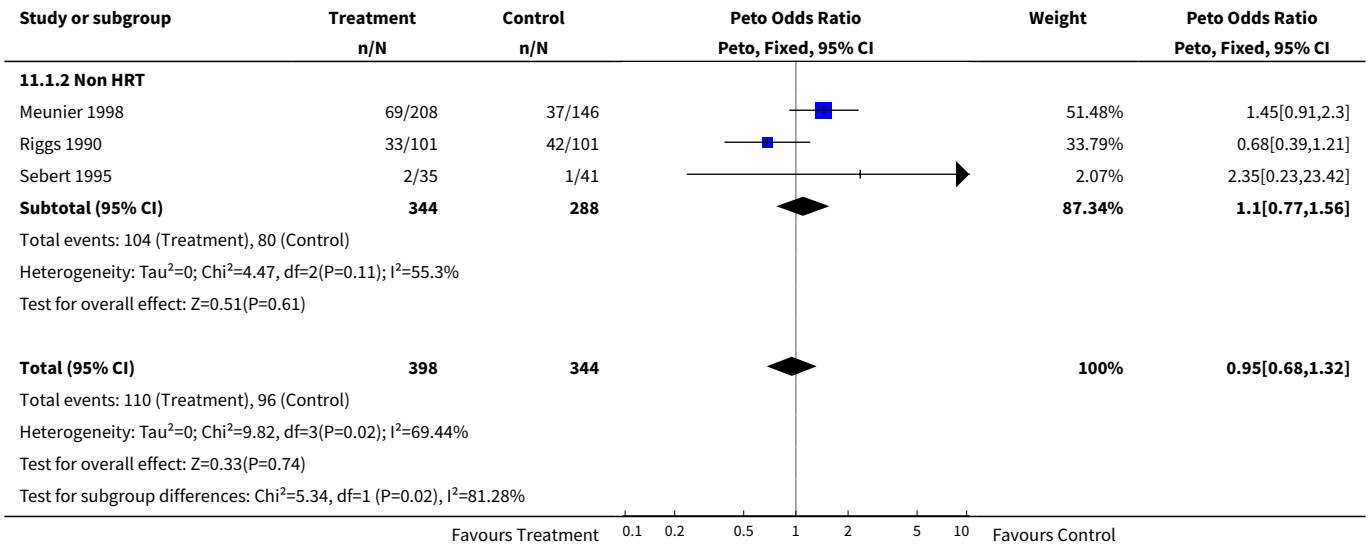
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 HRT	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.13, 0.86]
1.2 Non HRT	3	632	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.77, 1.56]
2 No. People with new vertebral fractures 4 years	5	646	Peto Odds 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 fractures 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 fractures 2 years	1	354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.65, 2.30]

Outcome or subgroup title	No. of studies	No. of participants	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 fractures 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]

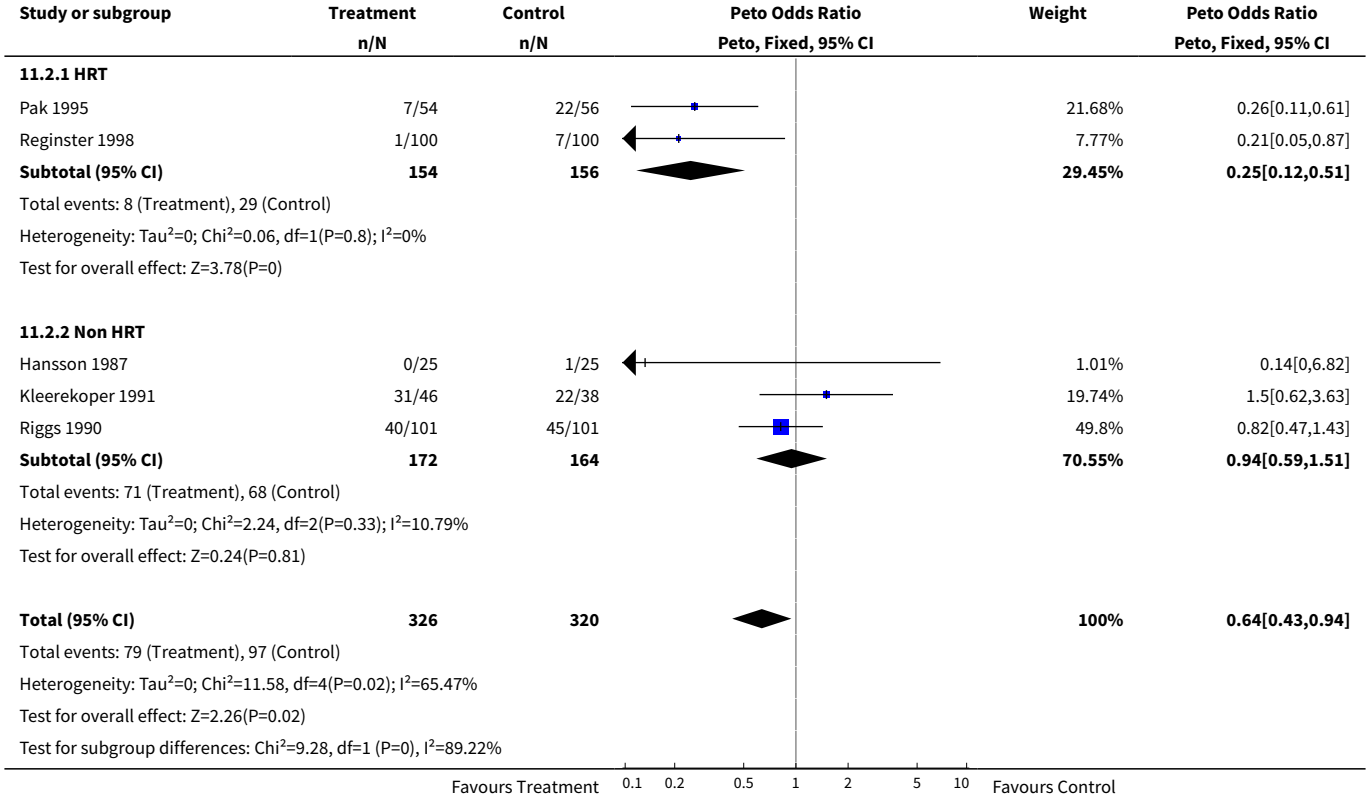
Analysis 11.1. Comparison 11 Subgroup HRT/non HRT, Outcome 1 No. People with new vertebral fractures-2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.28(P=0.02)					





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



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

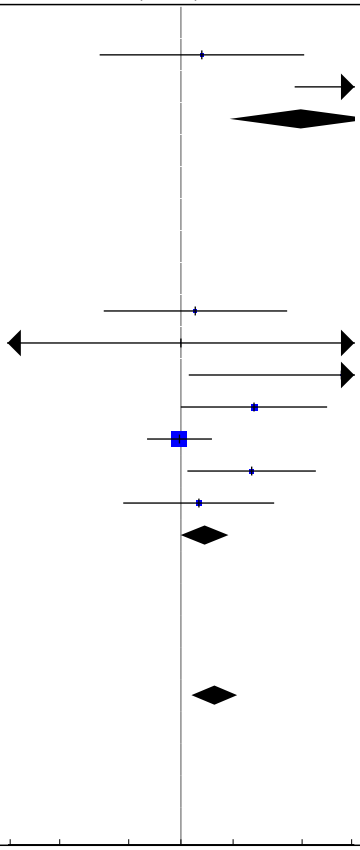
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.3.1 HRT							
Pak 1995	48	109.6 (10.3)	51	100.3 (6)		7.48%	9.34[6,12.68]
Reginster 1998	100	107.6 (4.6)	100	99.6 (3.4)		66.44%	8.04[6.92,9.16]
Subtotal ***	**148**		**151**			**73.92%**	**8.17[7.11,9.23]**
Heterogeneity: Tau²=0; Chi²=0.52, df=1(P=0.47); I²=0%							
Test for overall effect: Z=15.07(P<0.0001)							
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: Tau²=0; Chi²=60.47, df=4(P<0.0001); I²=93.39%							
Test for overall effect: Z=15.5(P<0.0001)							
Total ***	**466**		**536**			**100%**	**9.73[8.82,10.64]**
Heterogeneity: Tau²=0; Chi²=92.68, df=6(P<0.0001); I²=93.53%							
Test for overall effect: Z=20.87(P<0.0001)							
Test for subgroup differences: Chi²=31.69, df=1 (P<0.0001), I²=96.84%							

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

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.4.1 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: Tau²=0; Chi²=5.16, df=1(P=0.02); I²=80.62%							
Test for overall effect: Z=13.31(P<0.0001)							
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<0.0001)							
Total ***	**249**		**252**			**100%**	**14.87[13.39,16.35]**
Heterogeneity: Tau²=0; Chi²=180.91, df=2(P<0.0001); I²=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi²=175.75, df=1 (P<0.0001), I²=99.43%							

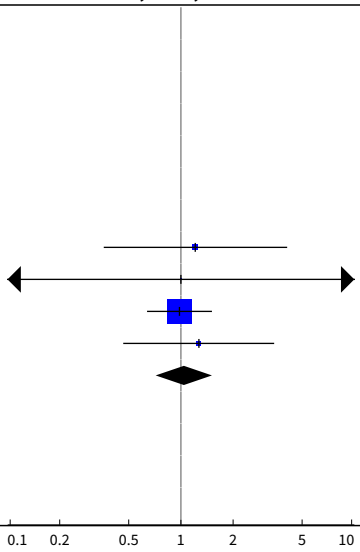
Analysis 11.5. Comparison 11 Subgroup HRT/non HRT, Outcome 5 GI minor overall.

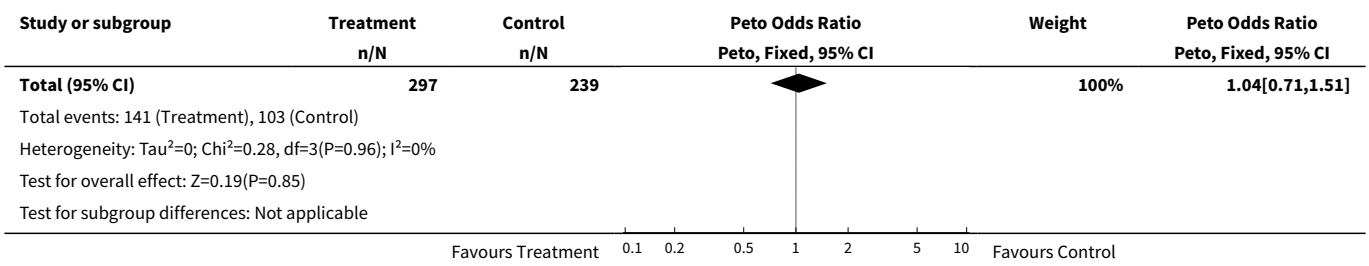
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
11.5.1 HRT					
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Riggs 1982	10/61	0/102		5.23%	16.93[4.53,63.26]
Subtotal (95% CI)	**115**	**158**		**10.16%**	**4.91[1.91,12.65]**
Total events: 15 (Treatment), 4 (Control)					
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 (Control)					
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 (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=6.29, df=1 (P=0.01), I^2=84.11%					



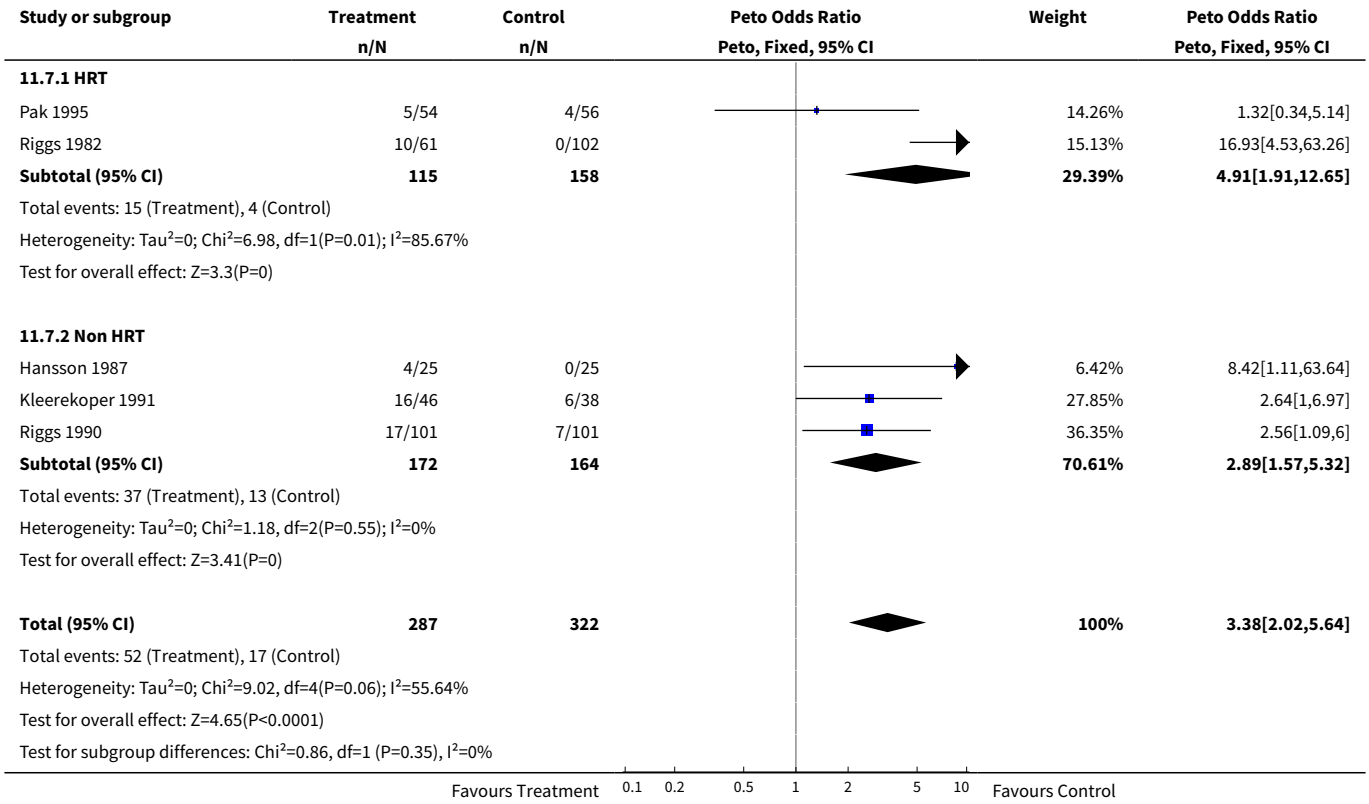
Analysis 11.6. Comparison 11 Subgroup HRT/non HRT, Outcome 6 GI minor 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
11.6.1 HRT					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.6.2 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 (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)					

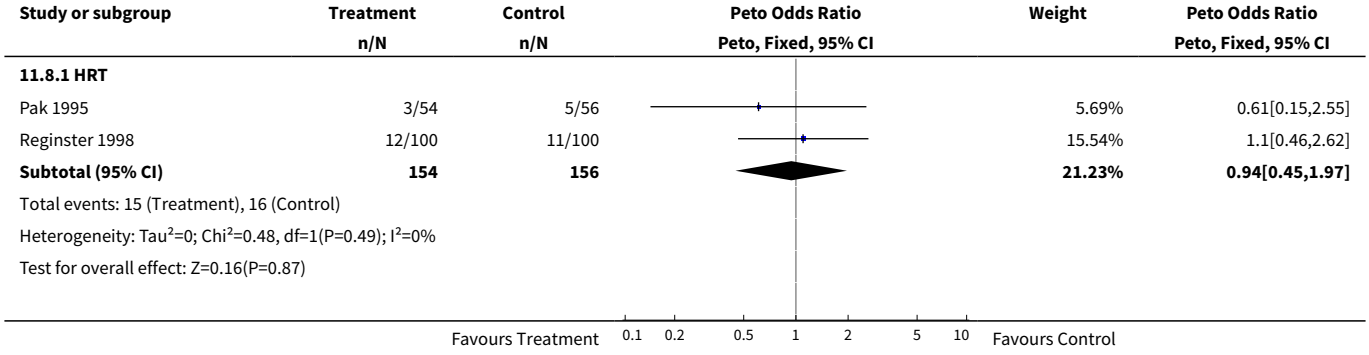


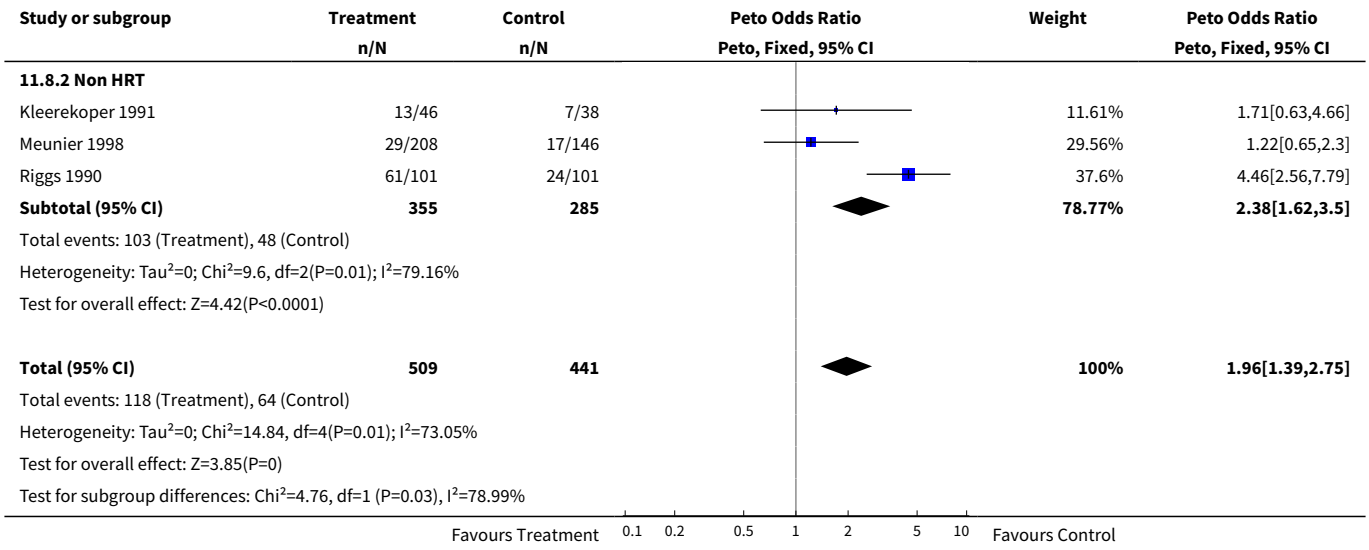


Analysis 11.7. Comparison 11 Subgroup HRT/non HRT, Outcome 7 GI minor 4 years.

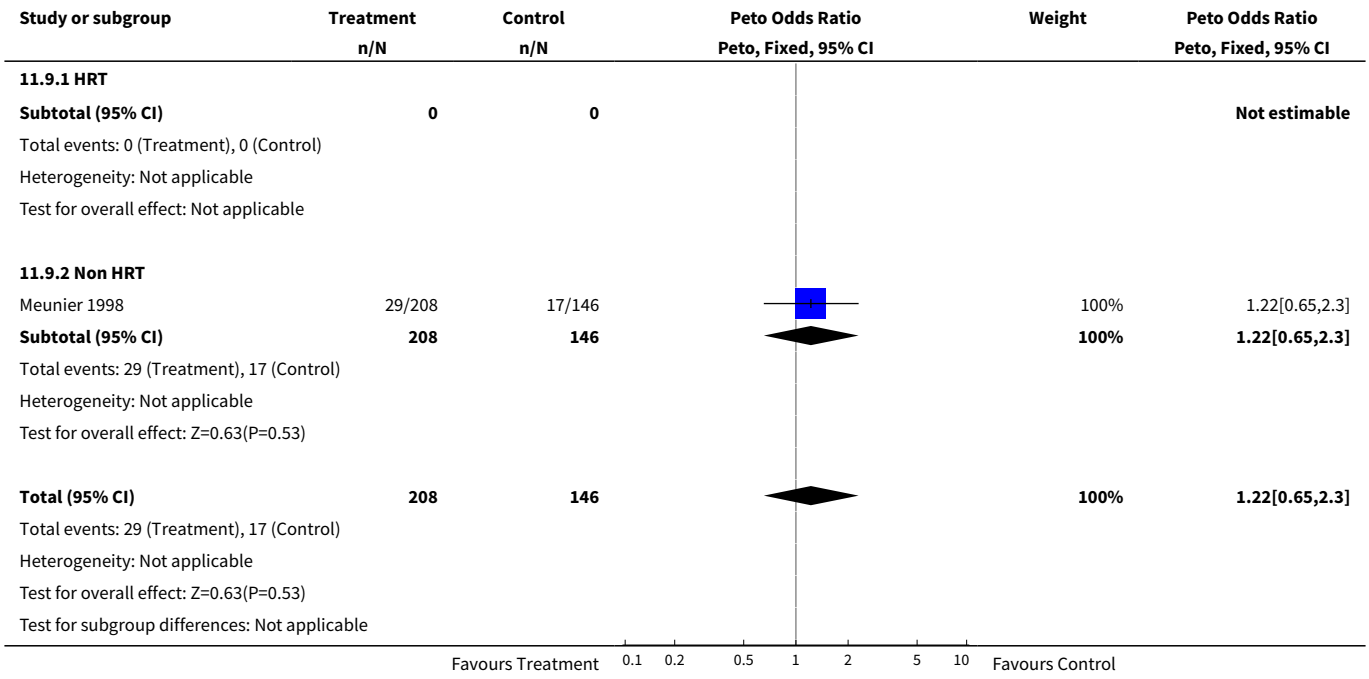


Analysis 11.8. Comparison 11 Subgroup HRT/non HRT, Outcome 8 Non vertebral fractures overall.

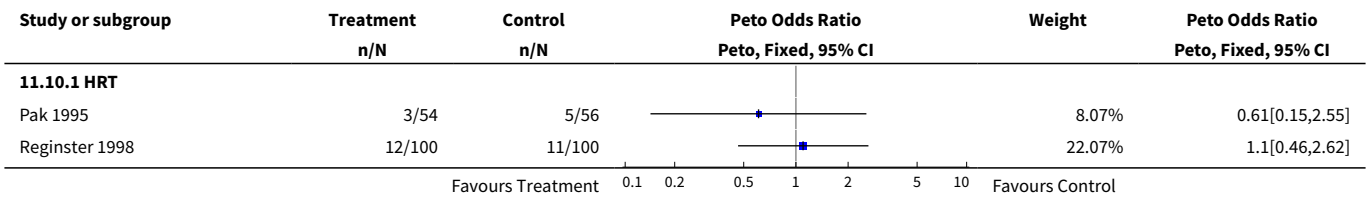


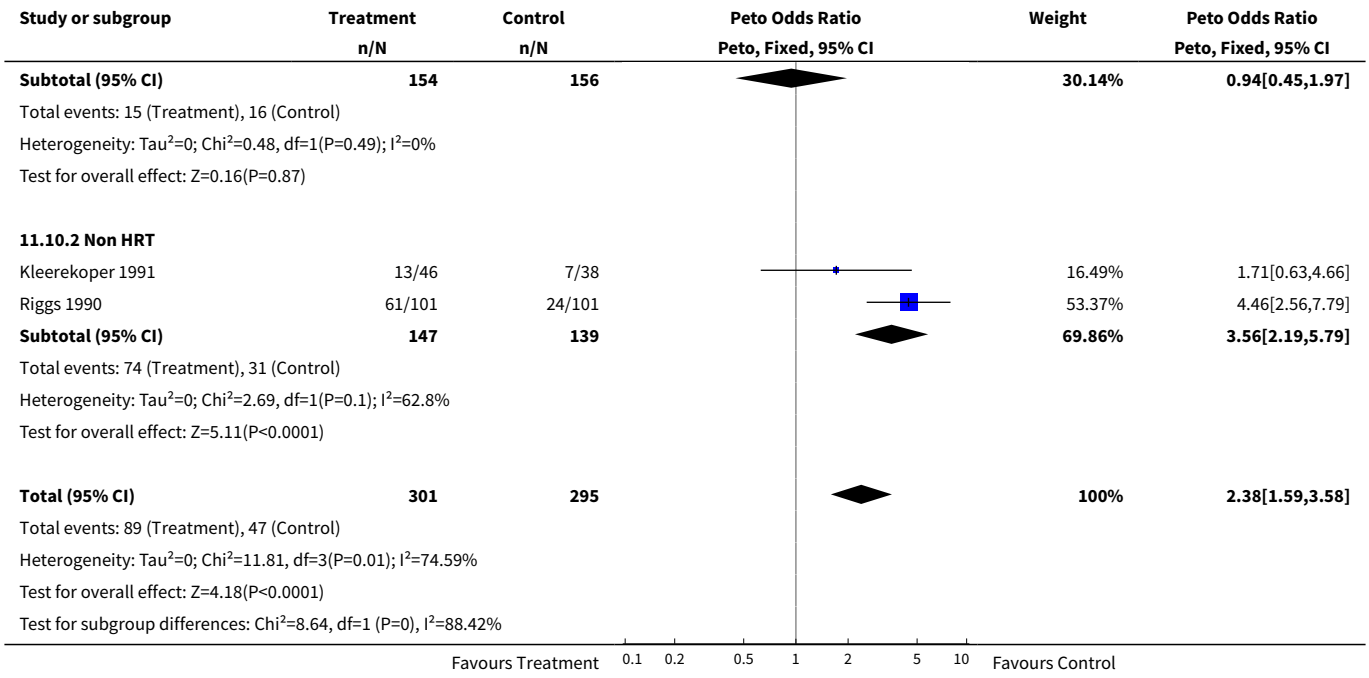


Analysis 11.9. Comparison 11 Subgroup HRT/non HRT, Outcome 9 Non vertebral fractures 2 years.

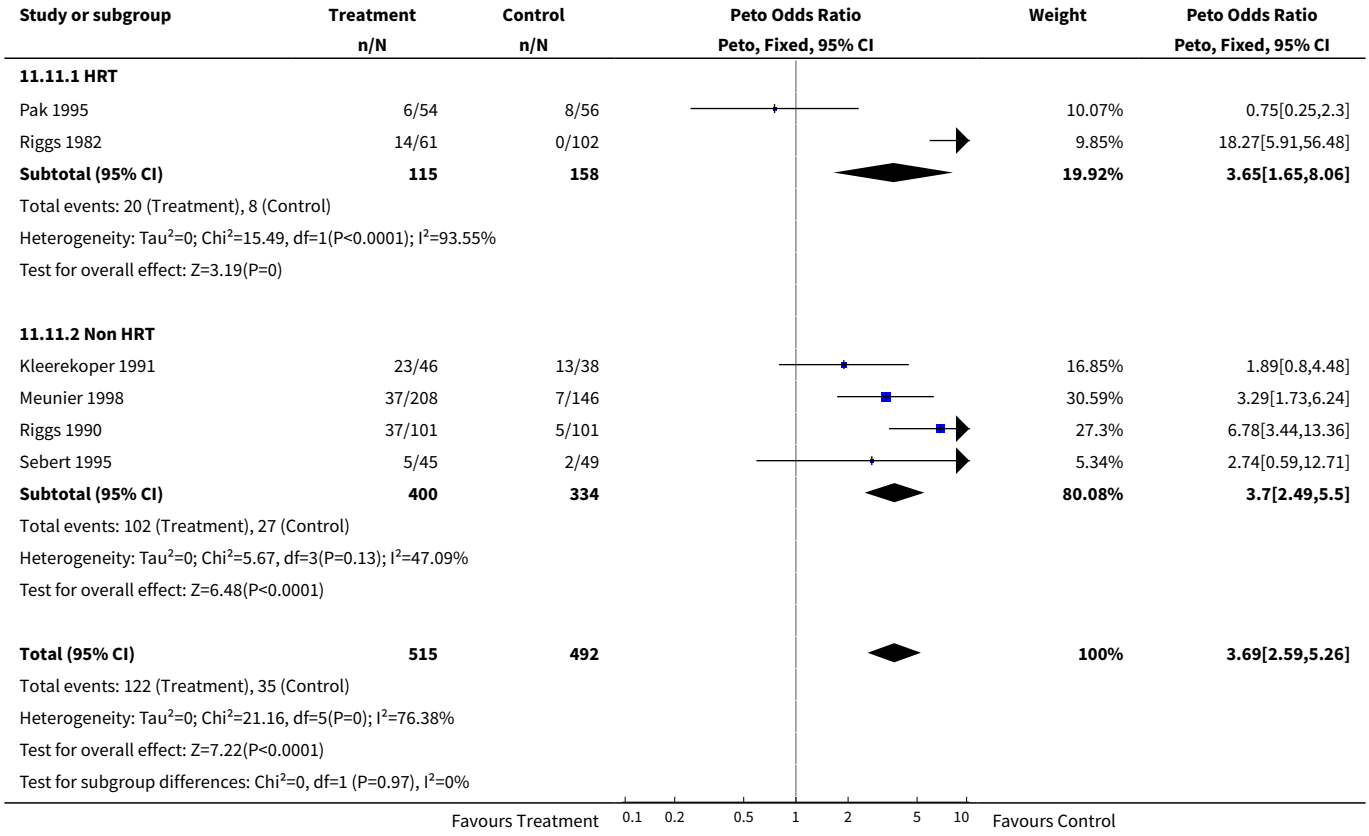


Analysis 11.10. Comparison 11 Subgroup HRT/non HRT, Outcome 10 Non vertebral fractures 4 years.

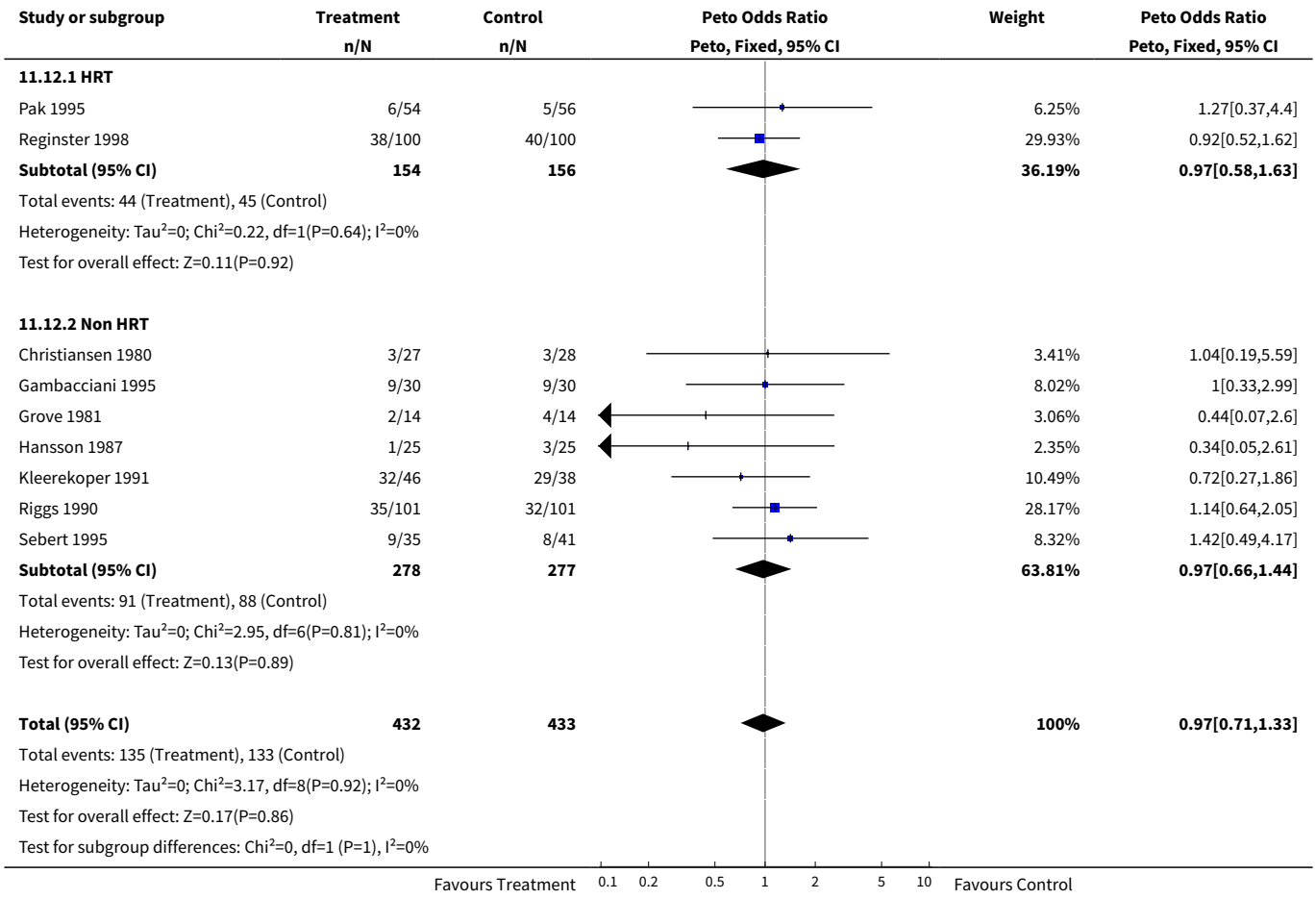




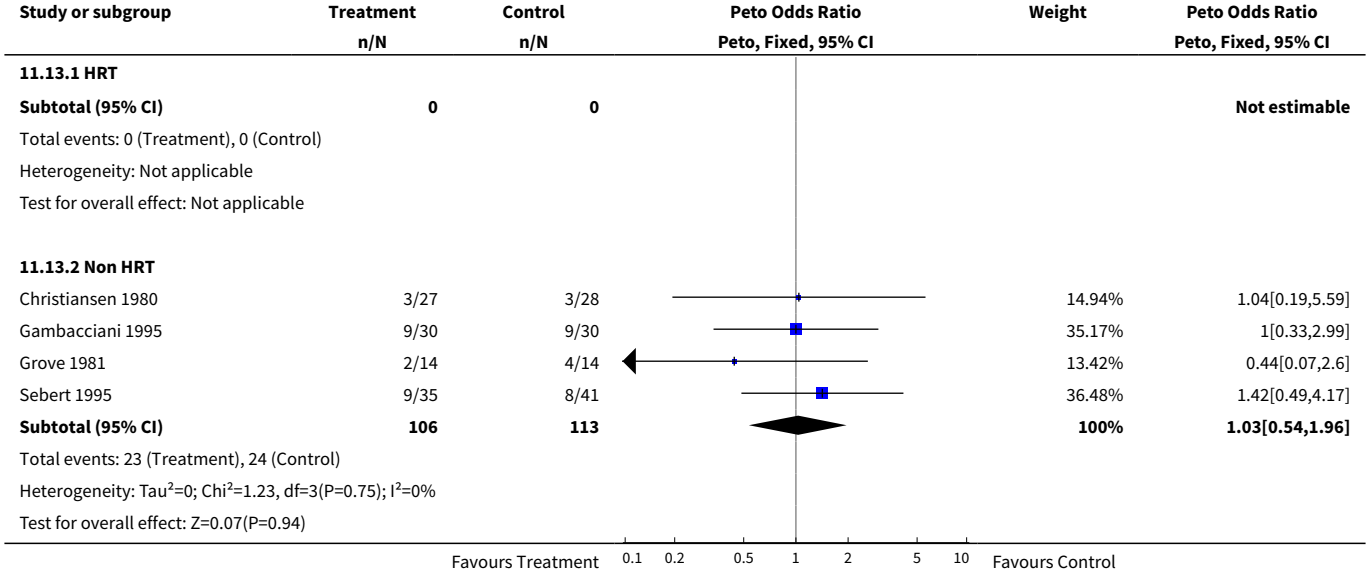
Analysis 11.11. Comparison 11 Subgroup HRT/non HRT, Outcome 11 Lower limb pain syndrome.

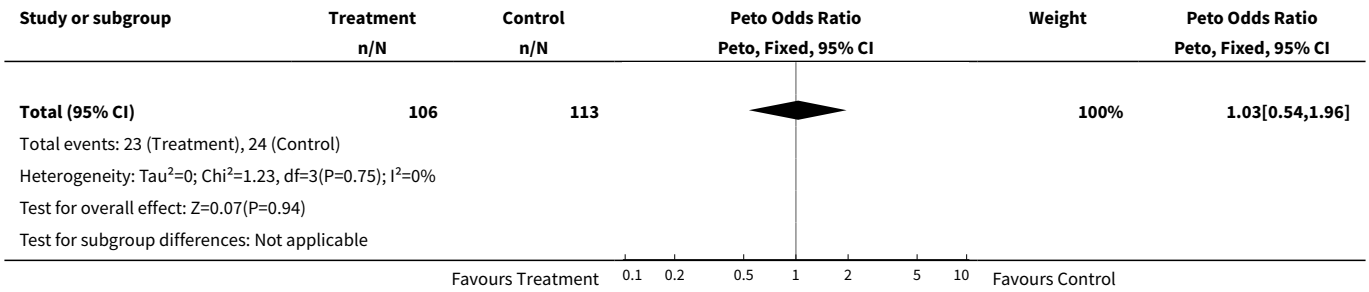


Analysis 11.12. Comparison 11 Subgroup HRT/non HRT, Outcome 12 Withdrawals and dropouts overall.

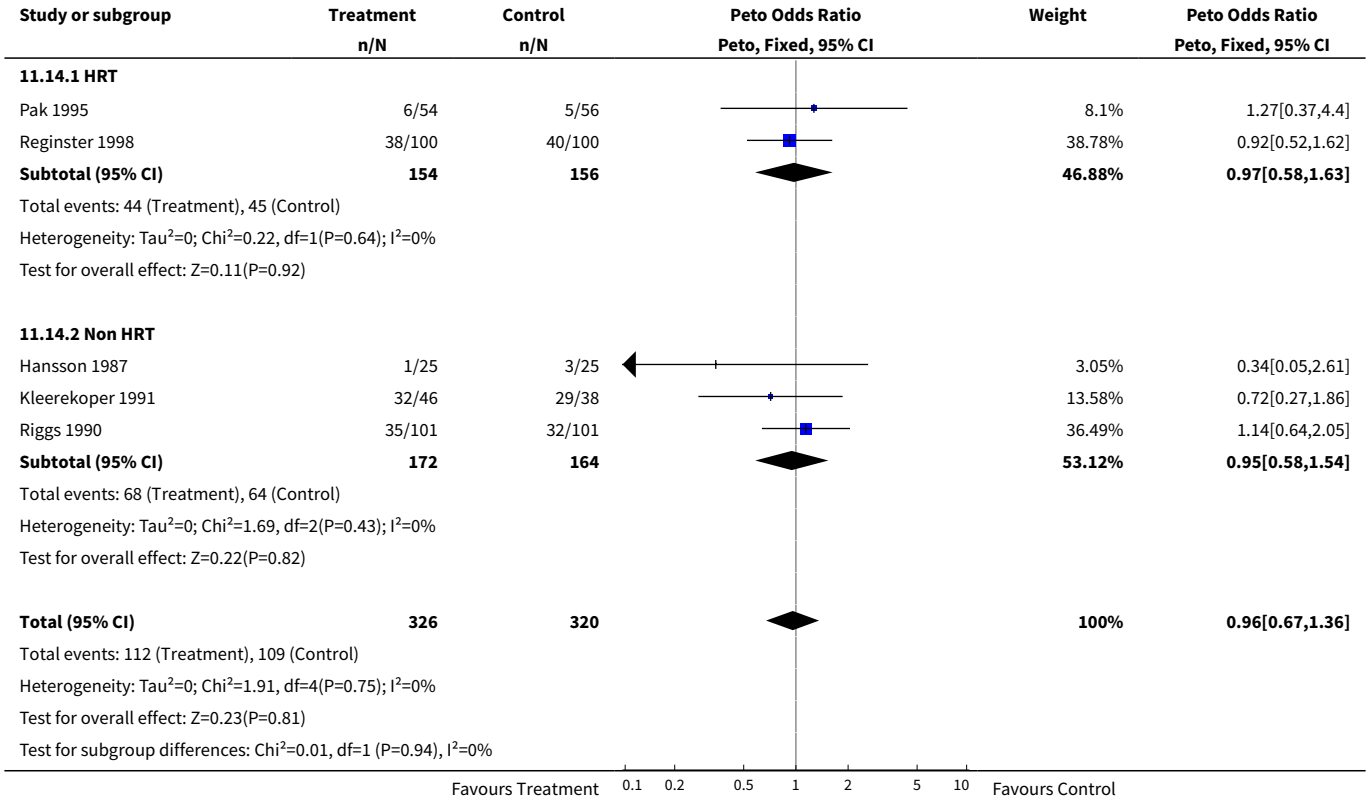


Analysis 11.13. Comparison 11 Subgroup HRT/non HRT, Outcome 13 Withdrawals and dropouts 2 years.





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



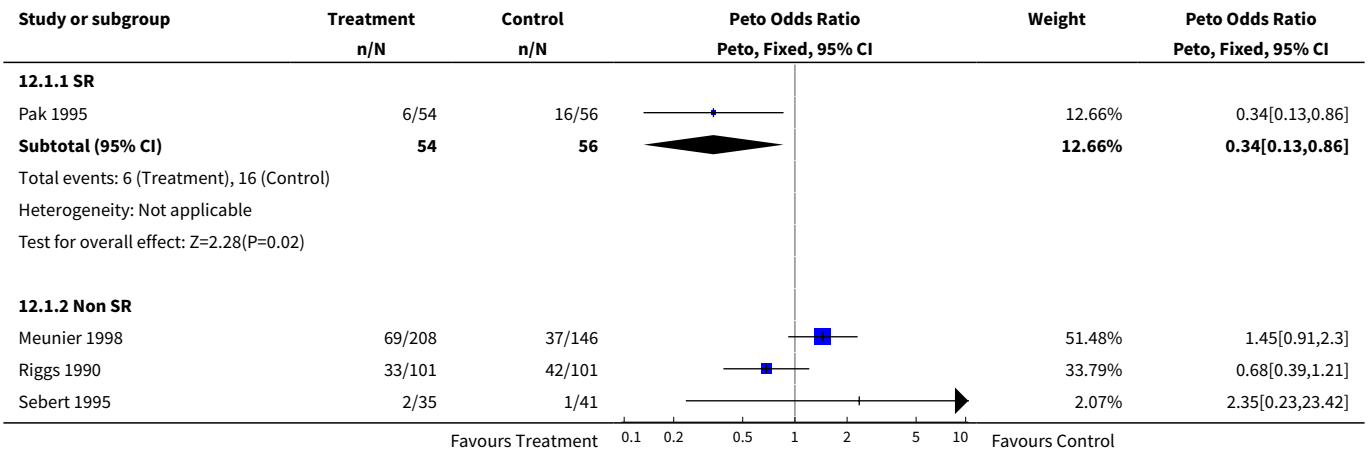
Comparison 12. Subgroup SR/non SR

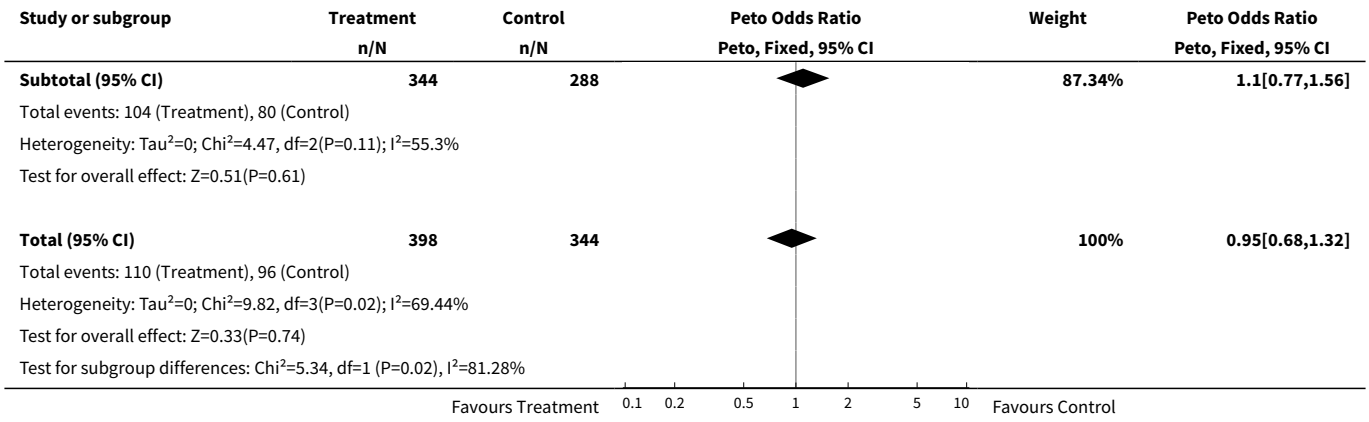
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures-2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.13, 0.86]
1.2 Non SR	3	632	Peto Odds Ratio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

Outcome or subgroup title	No. of studies	No. of participants	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 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 fractures 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 fractures 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]

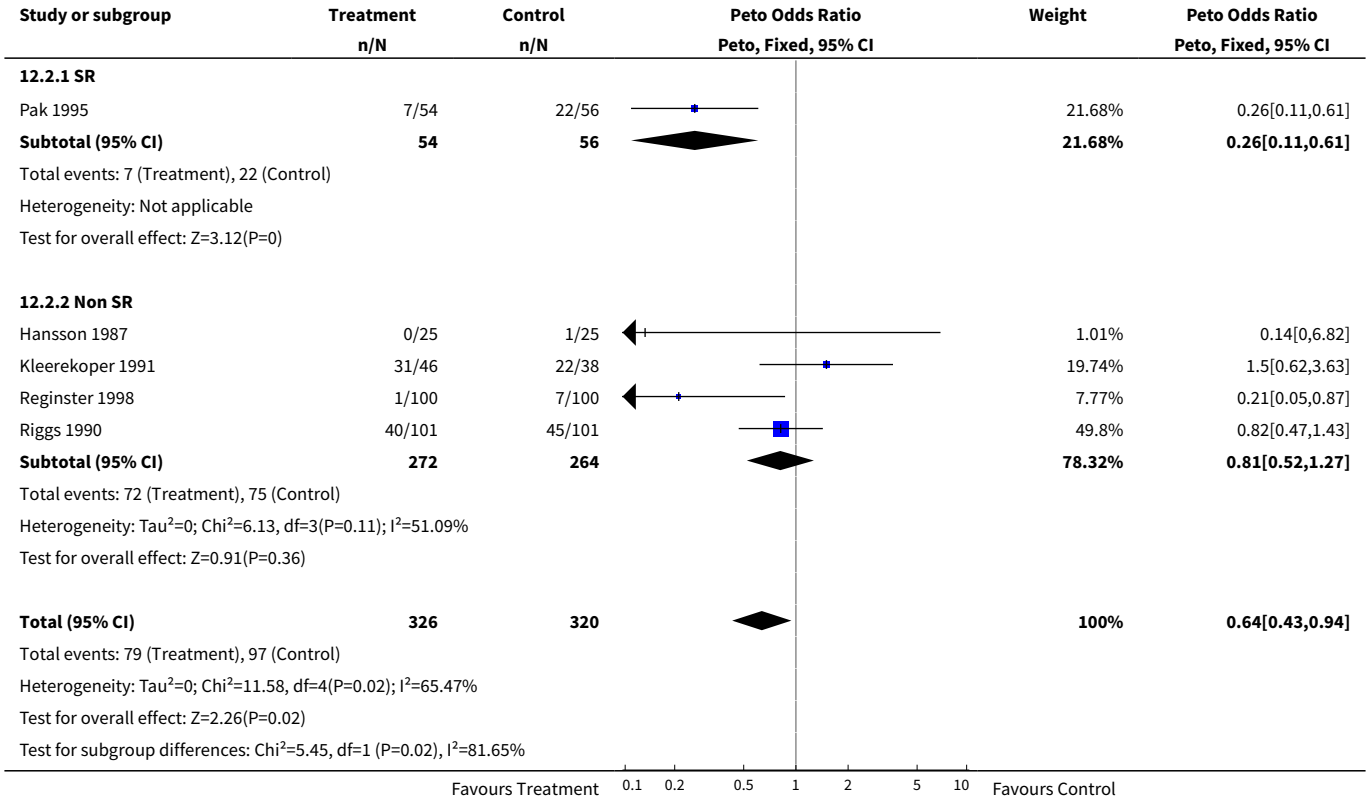
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Non vertebral fractures 4 years	4	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.59, 3.58]
10.1 SR	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.15, 2.55]
10.2 Non SR	3	486	Peto Odds Ratio (Peto, Fixed, 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.

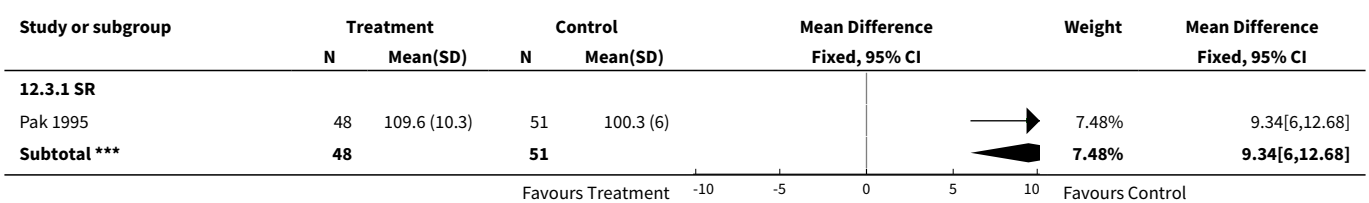


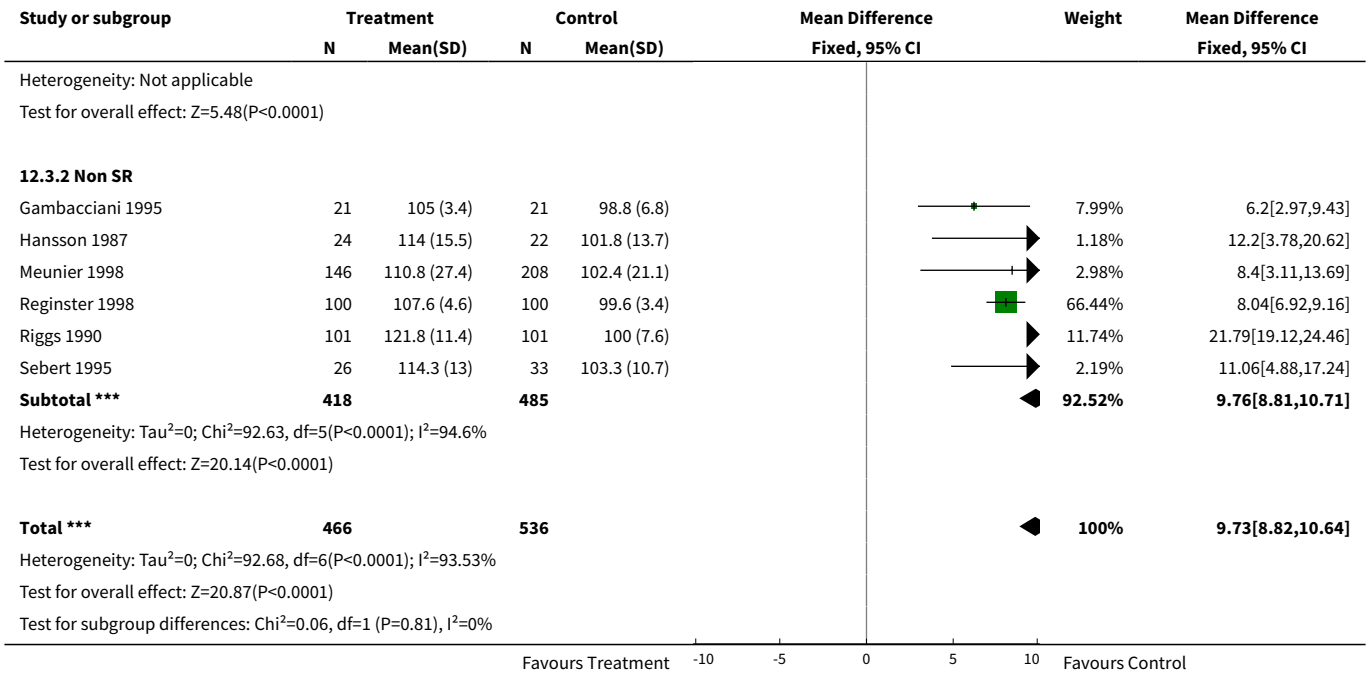


Analysis 12.2. Comparison 12 Subgroup SR/non SR, Outcome 2 No. People with new vertebral fractures 4 years.



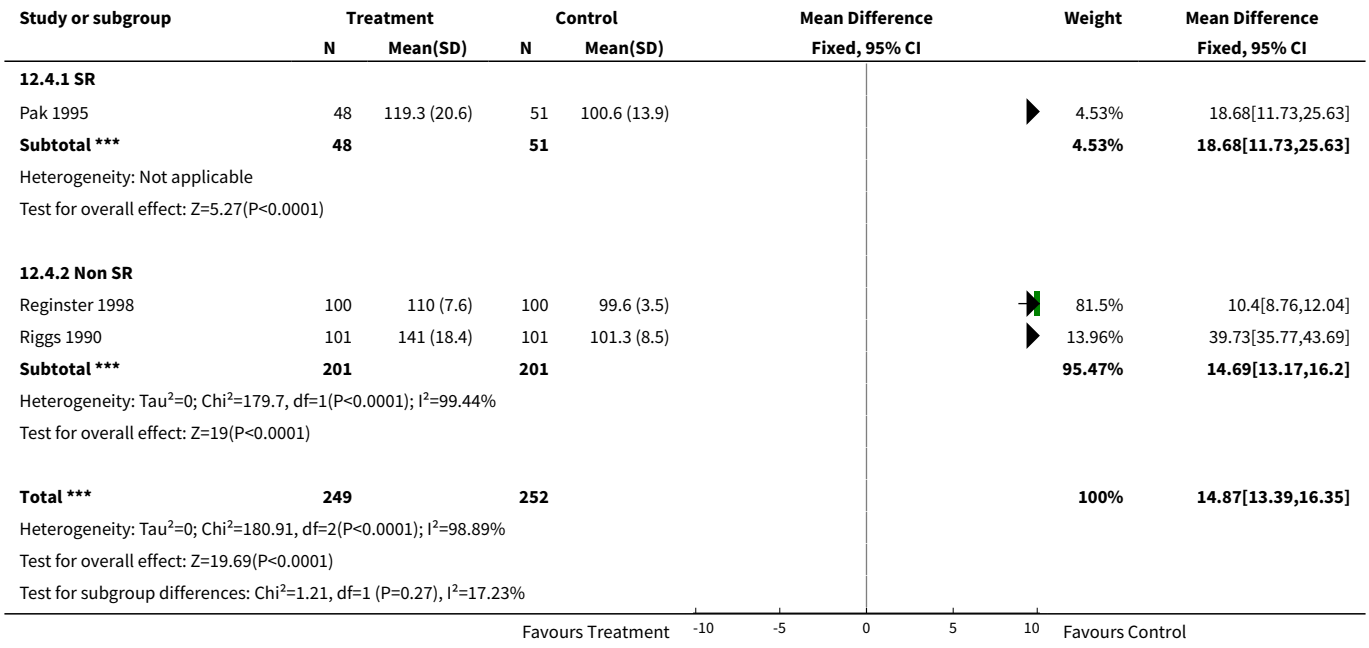
Analysis 12.3. Comparison 12 Subgroup SR/non SR, Outcome 3 Lumbar BMD % 2 years from baseline.





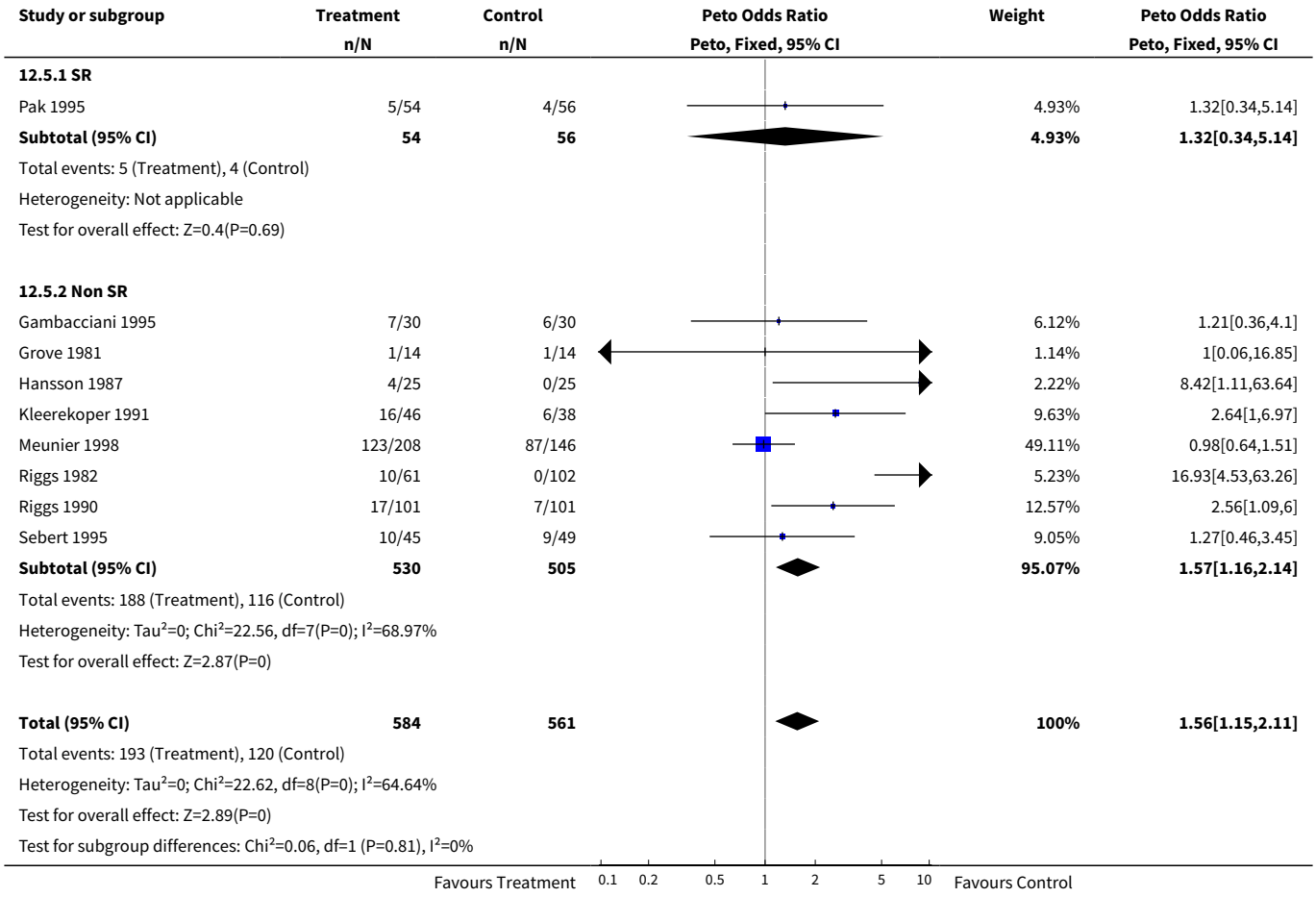
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=5.48(P<0.0001)							
12.3.2 Non SR							
Gambacciani 1995	21	105 (3.4)	21	98.8 (6.8)		7.99%	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, df=5(P<0.0001); I^2=94.6%							
Test for overall effect: Z=20.14(P<0.0001)							
Total ***	**466**		**536**			**100%**	**9.73[8.82,10.64]**
Heterogeneity: Tau^2=0; Chi^2=92.68, df=6(P<0.0001); I^2=93.53%							
Test for overall effect: Z=20.87(P<0.0001)							
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%							

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



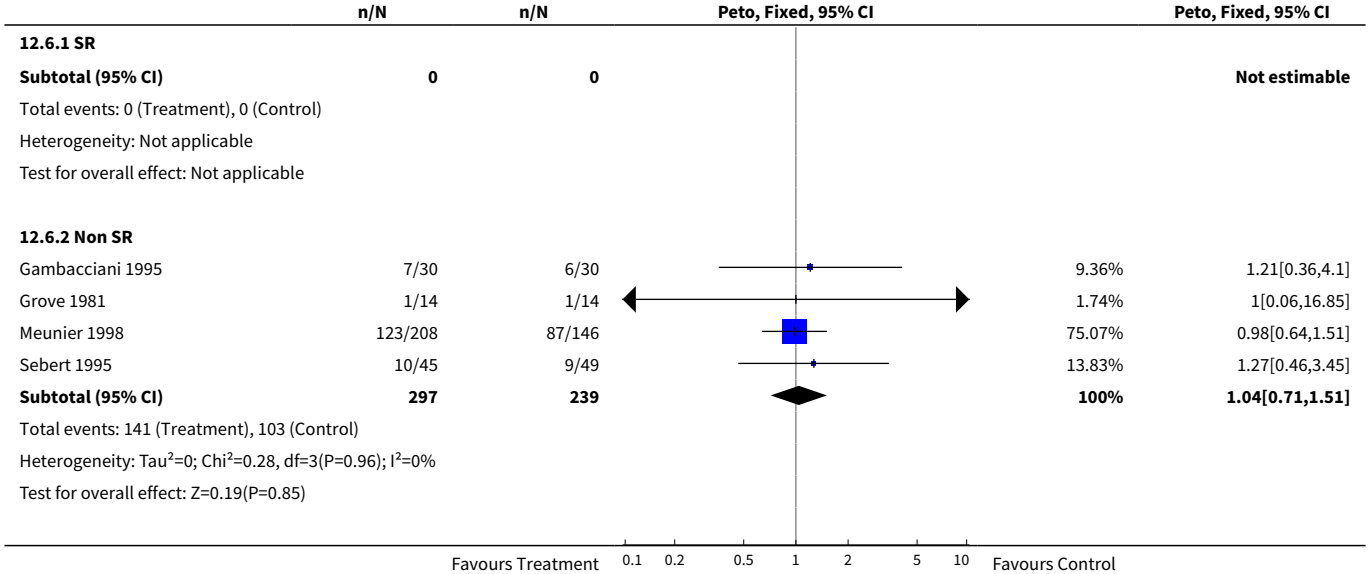
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
12.4.1 SR							
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)		4.53%	18.68[11.73,25.63]
Subtotal ***	**48**		**51**			**4.53%**	**18.68[11.73,25.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.27(P<0.0001)							
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<0.0001); 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, df=2(P<0.0001); I^2=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi^2=1.21, df=1 (P=0.27), I^2=17.23%							

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

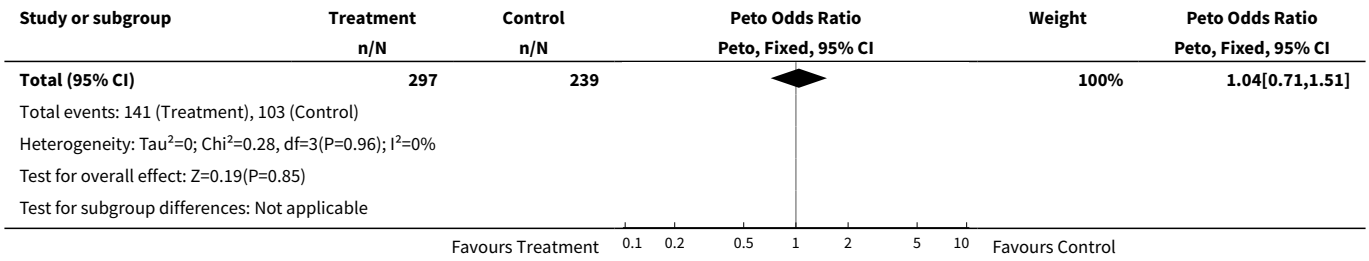


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
12.5.1 SR					
Pak 1995	5/54	4/56		4.93%	1.32[0.34,5.14]
Subtotal (95% CI)	**54**	**56**		**4.93%**	**1.32[0.34,5.14]**
Total events: 5 (Treatment), 4 (Control)					
Heterogeneity: 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 (Control)					
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 (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=0.06, df=1 (P=0.81), I^2=0%					

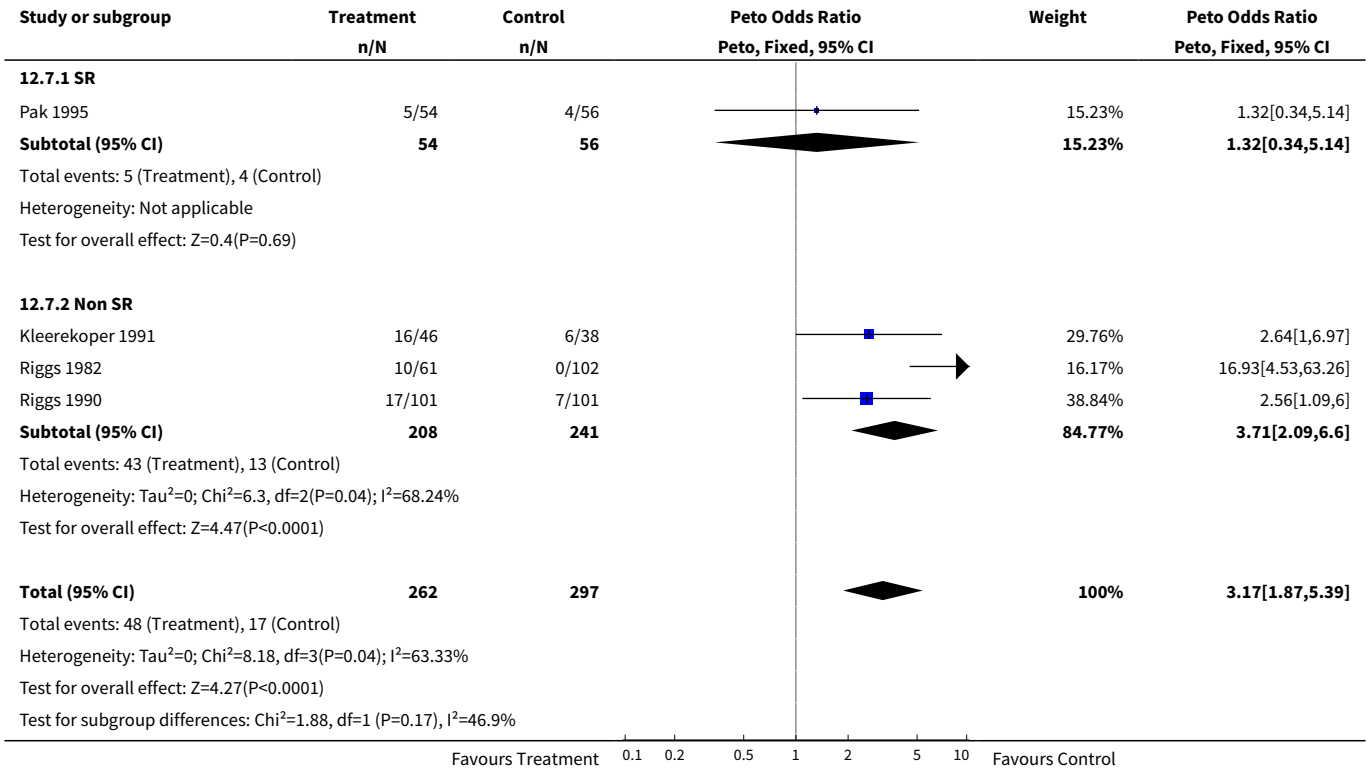
Analysis 12.6. Comparison 12 Subgroup SR/non SR, Outcome 6 GI minor 2 years.



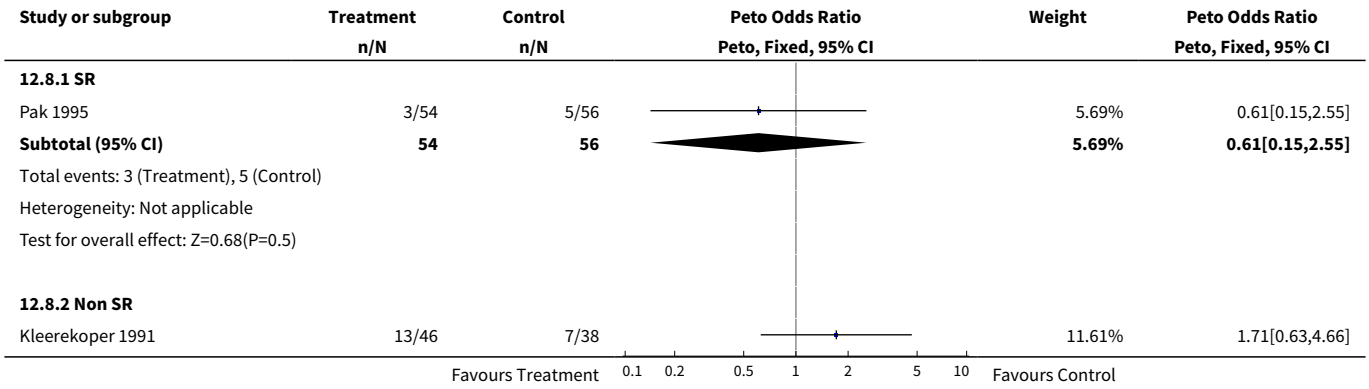
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
12.6.1 SR					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
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 (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)					

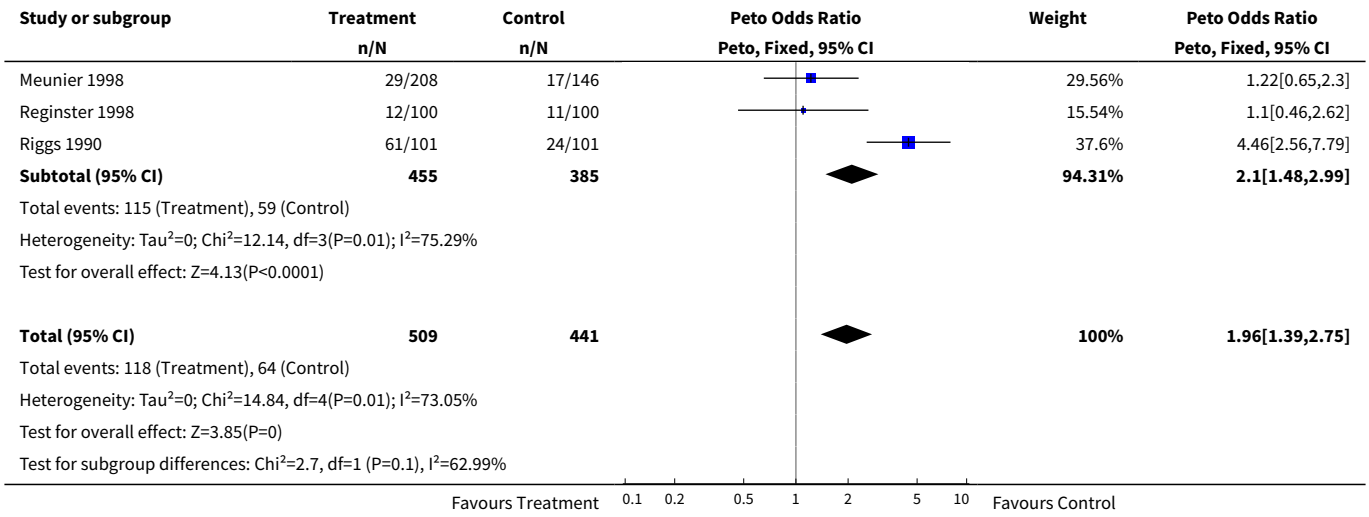


Analysis 12.7. Comparison 12 Subgroup SR/non SR, Outcome 7 GI minor 4 years.

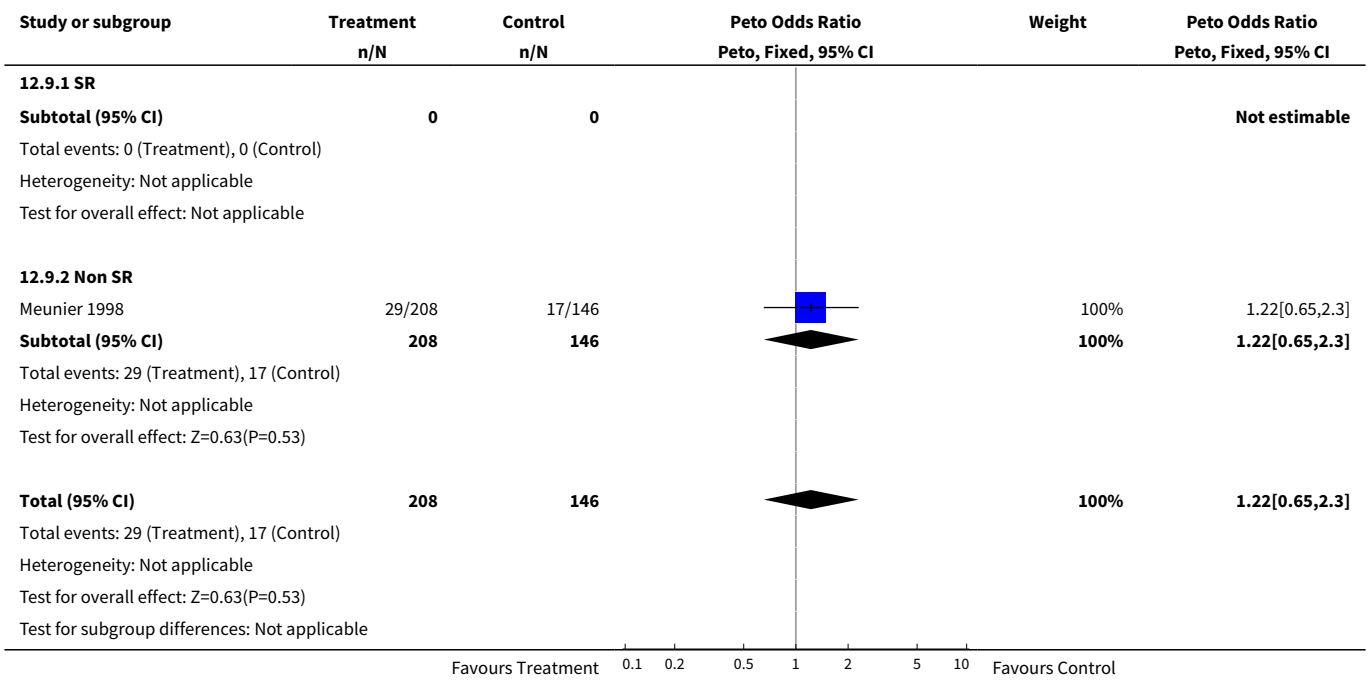


Analysis 12.8. Comparison 12 Subgroup SR/non SR, Outcome 8 Non vertebral fractures overall.

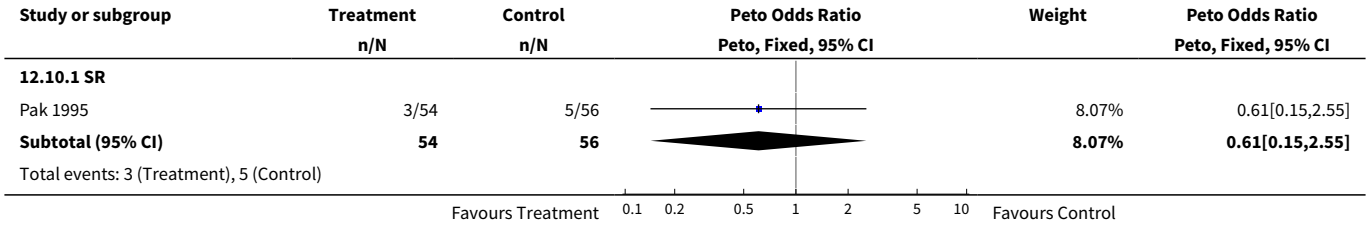


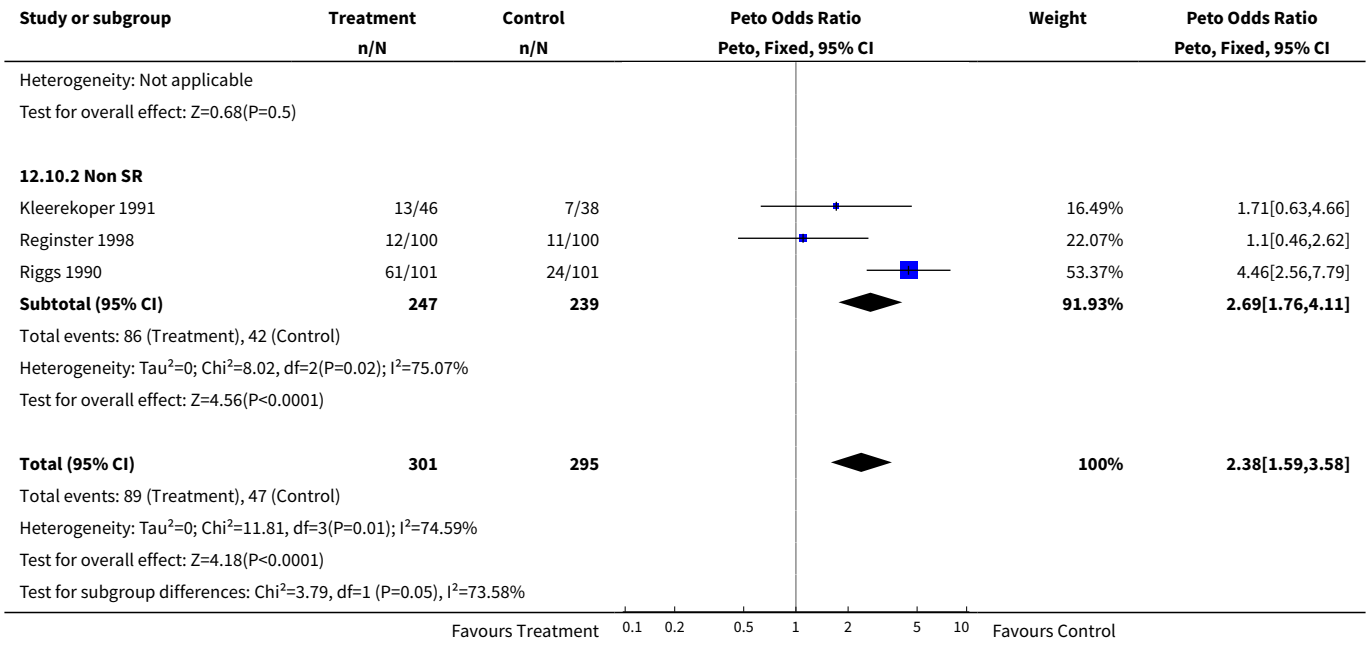


Analysis 12.9. Comparison 12 Subgroup SR/non SR, Outcome 9 Non vertebral fractures 2 years.

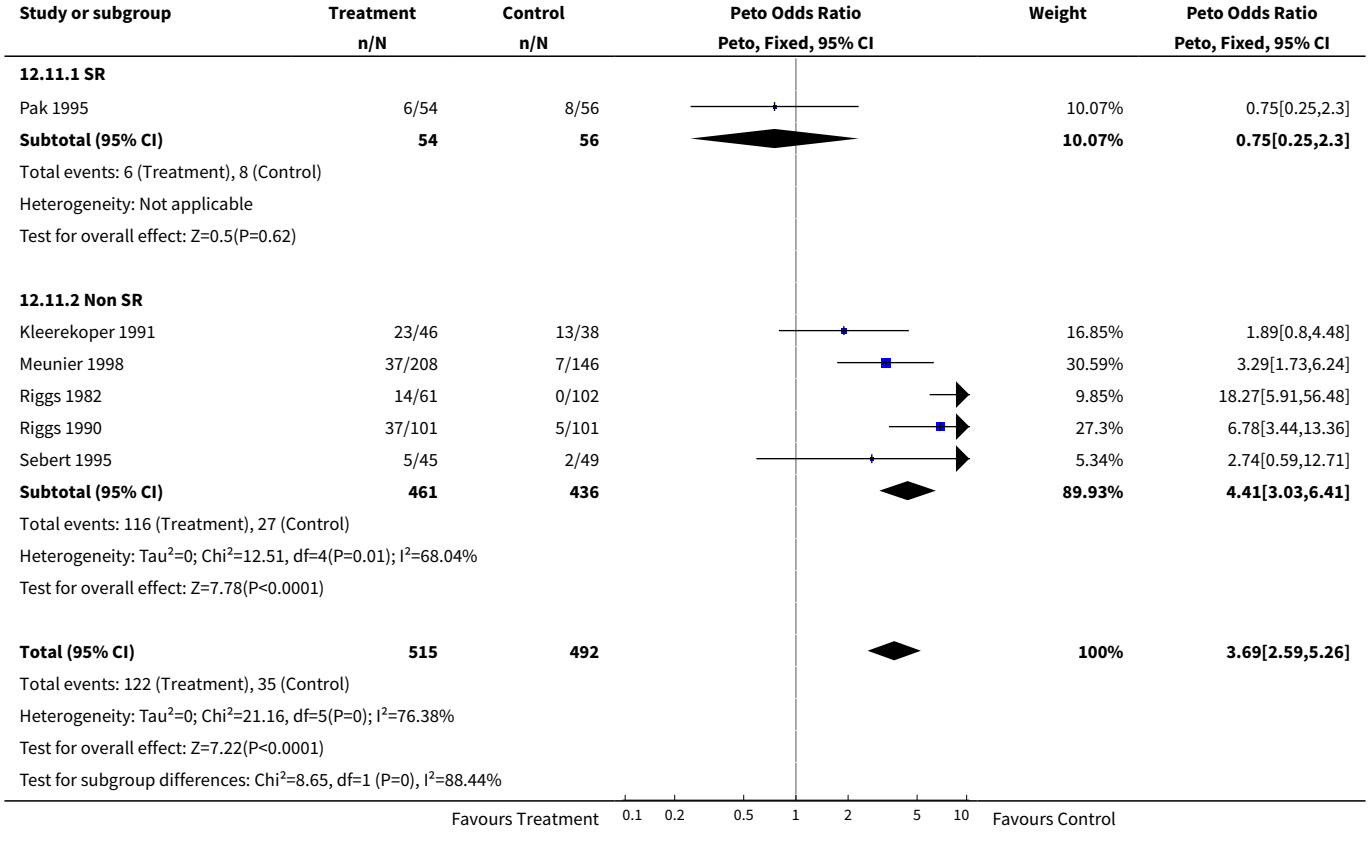


Analysis 12.10. Comparison 12 Subgroup SR/non SR, Outcome 10 Non vertebral fractures 4 years.



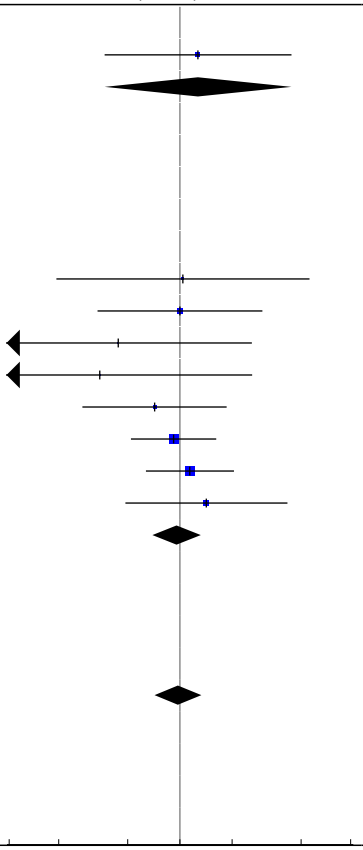


Analysis 12.11. Comparison 12 Subgroup SR/non SR, Outcome 11 Lower limb pain syndrome.



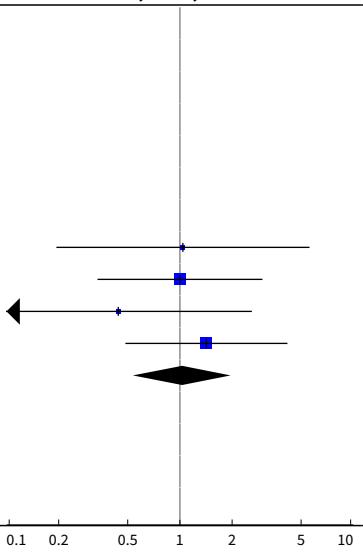
Analysis 12.12. Comparison 12 Subgroup SR/non SR, Outcome 12 Withdrawals and dropouts overall.

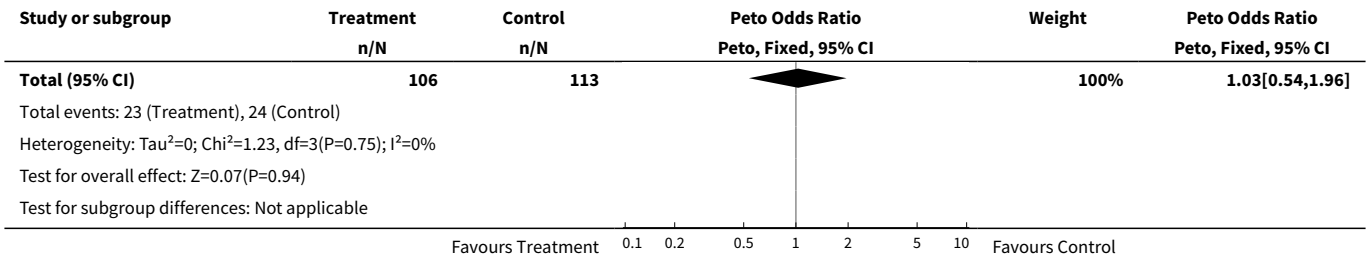
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
12.12.1 SR					
Pak 1995	6/54	5/56		6.25%	1.27[0.37,4.4]
Subtotal (95% CI)	**54**	**56**		**6.25%**	**1.27[0.37,4.4]**
Total events: 6 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					
12.12.2 Non SR					
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]
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, df=7(P=0.89); I^2=0%					
Test for overall effect: Z=0.27(P=0.78)					
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)					
Test for subgroup differences: Chi^2=0.19, df=1 (P=0.66), I^2=0%					



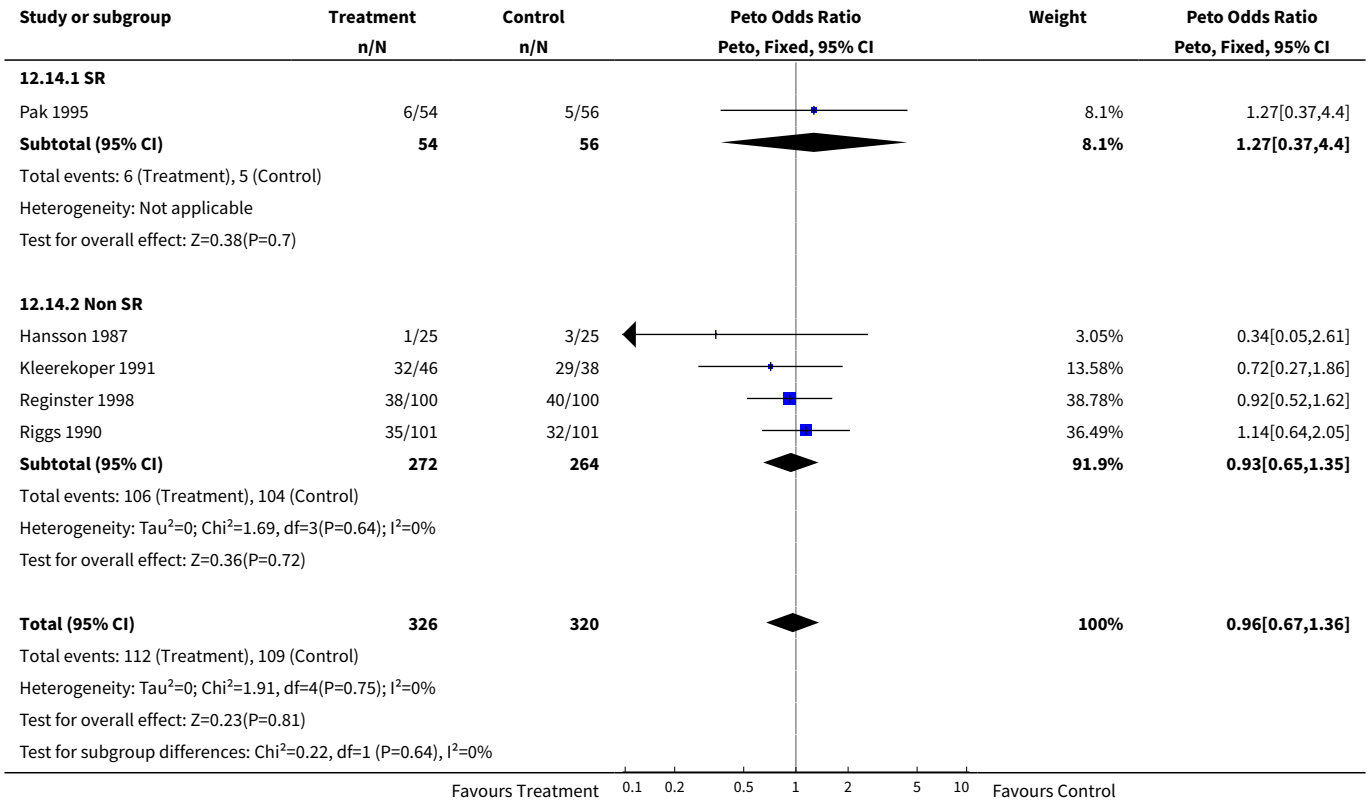
Analysis 12.13. Comparison 12 Subgroup SR/non SR, Outcome 13 Withdrawals and dropouts 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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 (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)					





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



Comparison 13. Subgroup Ca dosage and/or vit D

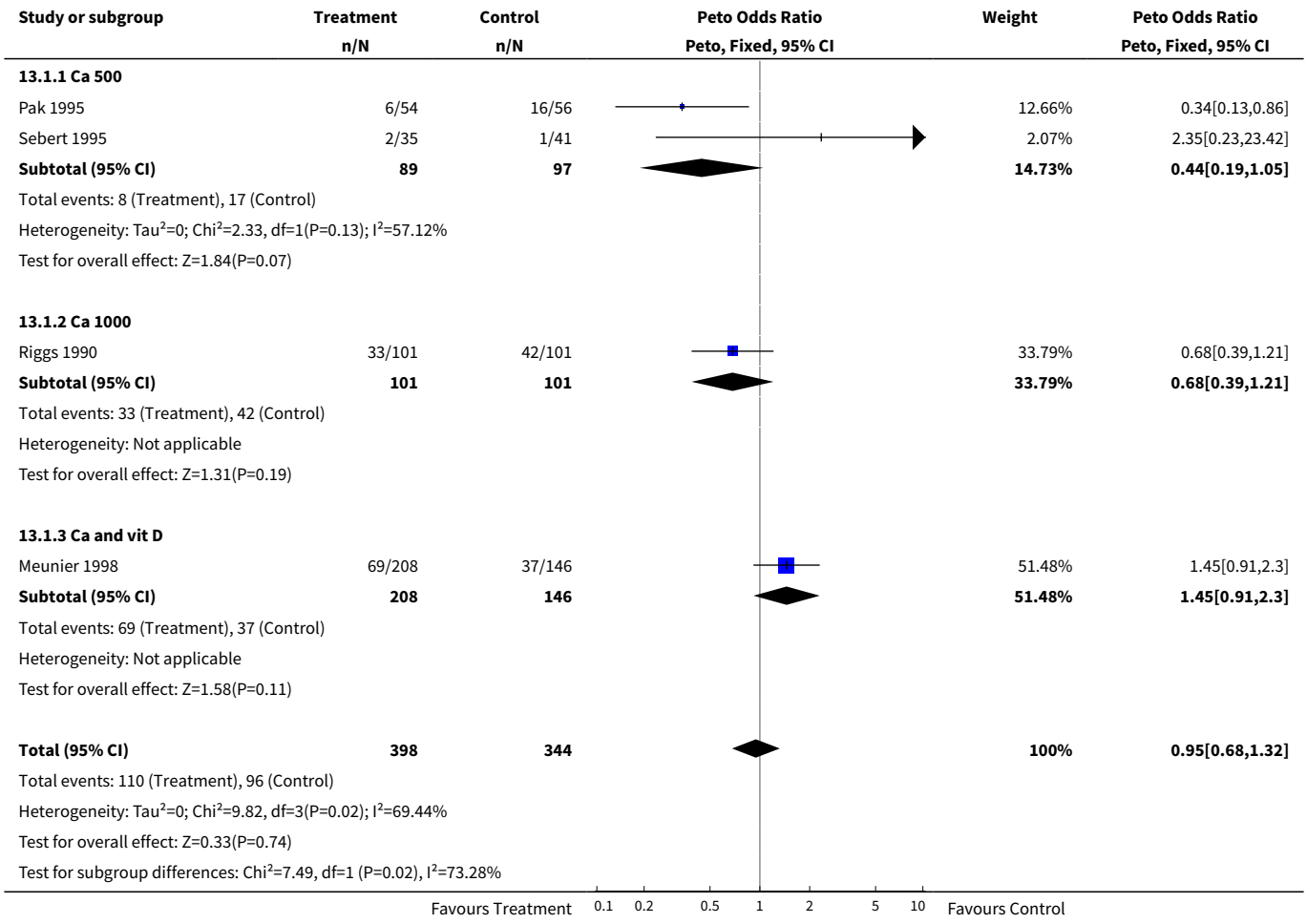
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. people with new vertebral fracture 2 years	4	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.68, 1.32]
1.1 Ca 500	2	186	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.19, 1.05]
1.2 Ca 1000	1	202	Peto Odds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

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]

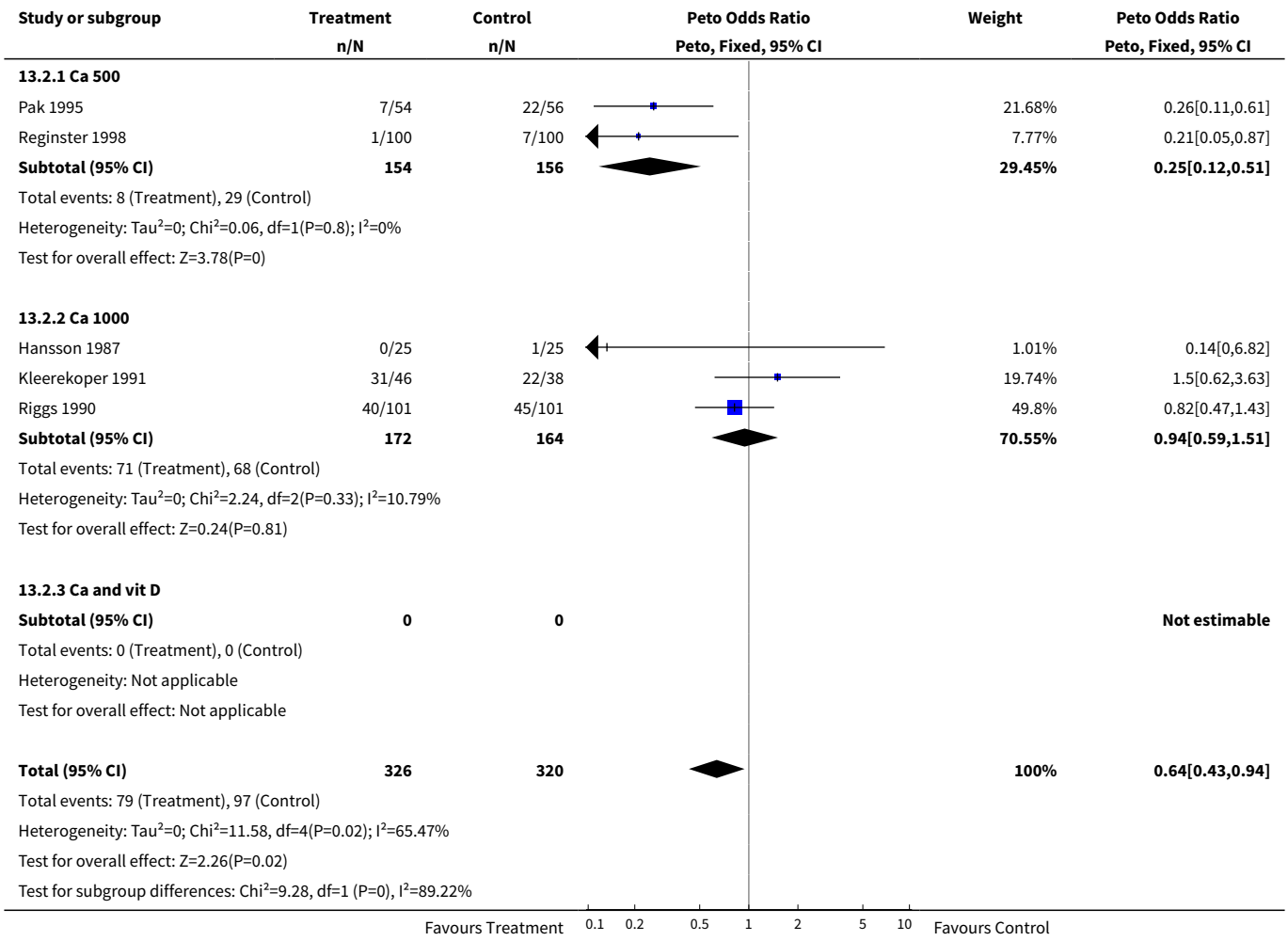
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Non vertebral fractures overall	5	950	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [1.39, 2.75]
8.1 Ca 500	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.15, 2.55]
8.2 Ca 1000	2	286	Peto Odds Ratio (Peto, 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 fractures 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 fractures 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]

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.

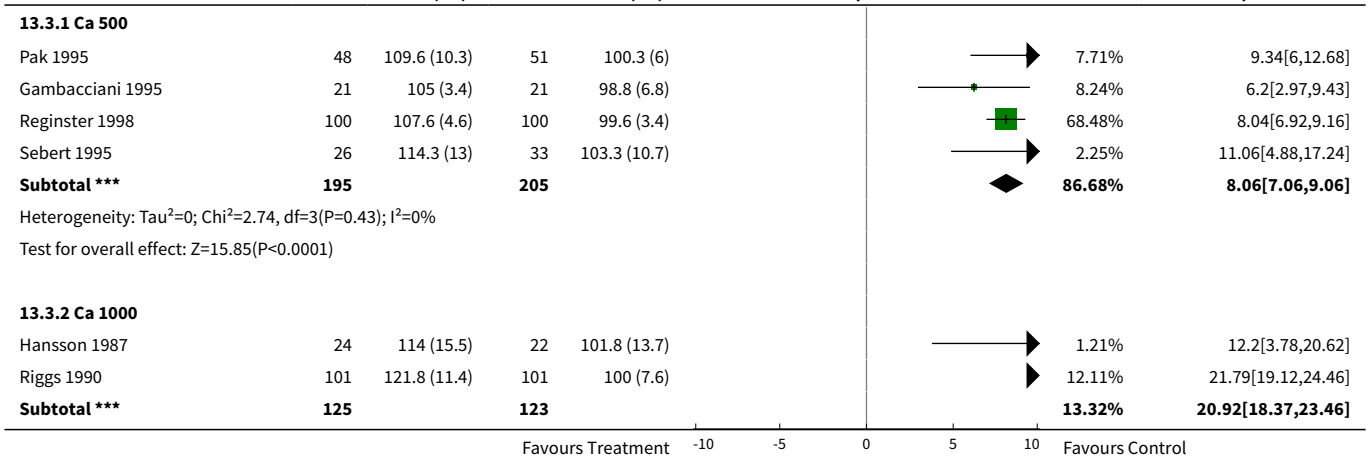


Analysis 13.2. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 2 No. people with new vertebral fracture 4 years.



Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 (Control)					
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 (Control)					
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 (Control)					
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=9.28, df=1 (P=0), I^2=89.22%					

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



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference 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); I^2=0%							
Test for overall effect: Z=15.85(P<0.0001)							
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]**

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=4.52, df=1(P=0.03); I²=77.9%							
Test for overall effect: Z=16.13(P<0.0001)							
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: Tau²=0; Chi²=92.43, df=5(P<0.0001); I²=94.59%							
Test for overall effect: Z=20.64(P<0.0001)							
Test for subgroup differences: Chi²=85.17, df=1 (P<0.0001), I²=98.83%							

Favours Treatment -10 -5 0 5 10 Favours Control

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

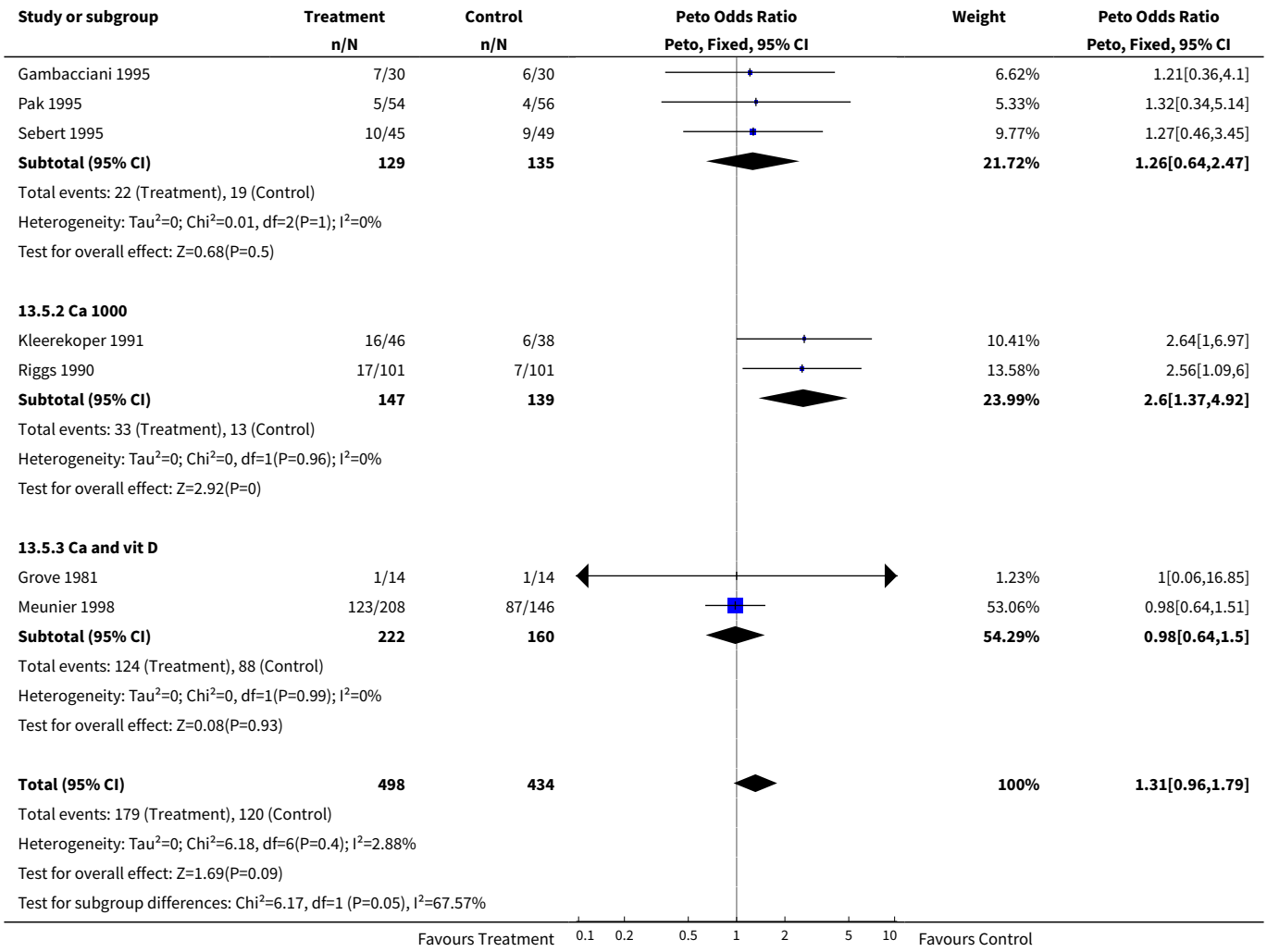
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
13.4.1 Ca 500							
Pak 1995	48	119.3 (20.6)	51	100.6 (13.9)		4.53%	18.68[11.73,25.63]
Reginster 1998	100	110 (7.6)	100	99.6 (3.5)		81.5%	10.4[8.76,12.04]
Subtotal ***	**148**		**151**			**86.04%**	**10.84[9.24,12.43]**
Heterogeneity: Tau²=0; Chi²=5.16, df=1(P=0.02); I²=80.62%							
Test for overall effect: Z=13.31(P<0.0001)							
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<0.0001)							
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: Tau²=0; Chi²=180.91, df=2(P<0.0001); I²=98.89%							
Test for overall effect: Z=19.69(P<0.0001)							
Test for subgroup differences: Chi²=175.75, df=1 (P<0.0001), I²=99.43%							

Favours Treatment -10 -5 0 5 10 Favours Control

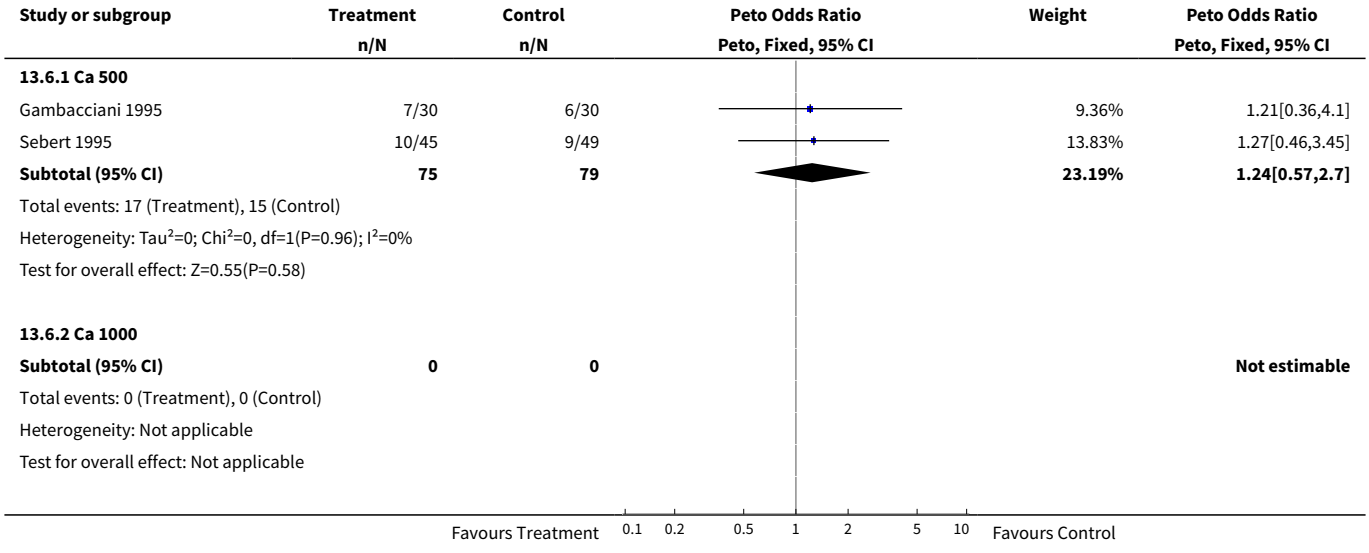
Analysis 13.5. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 5 GI minor overall.

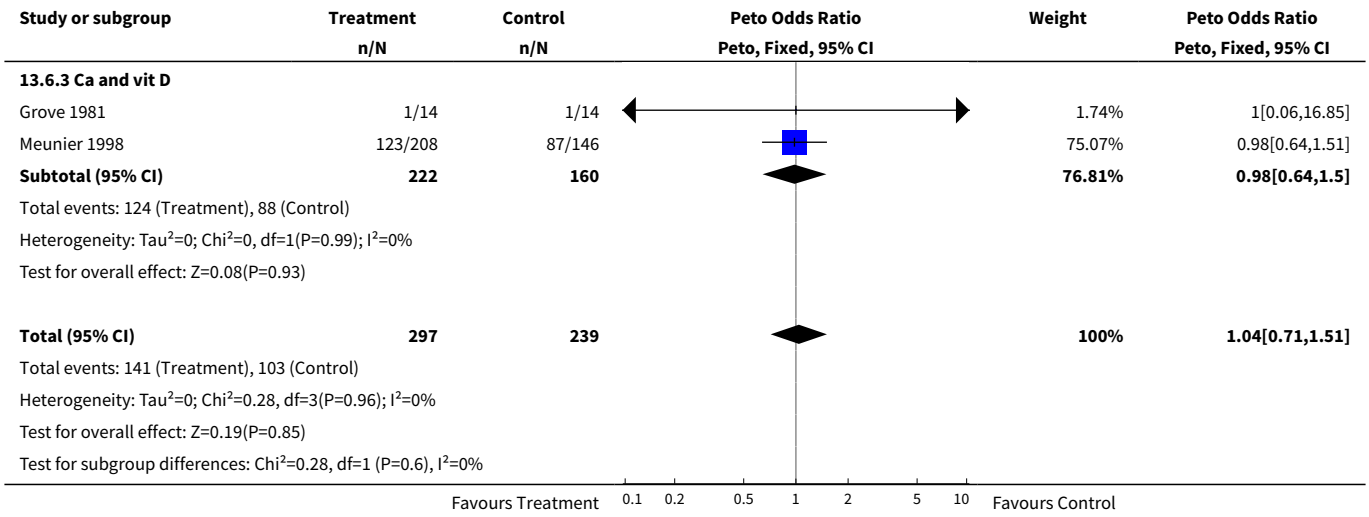
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
13.5.1 Ca 500					

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

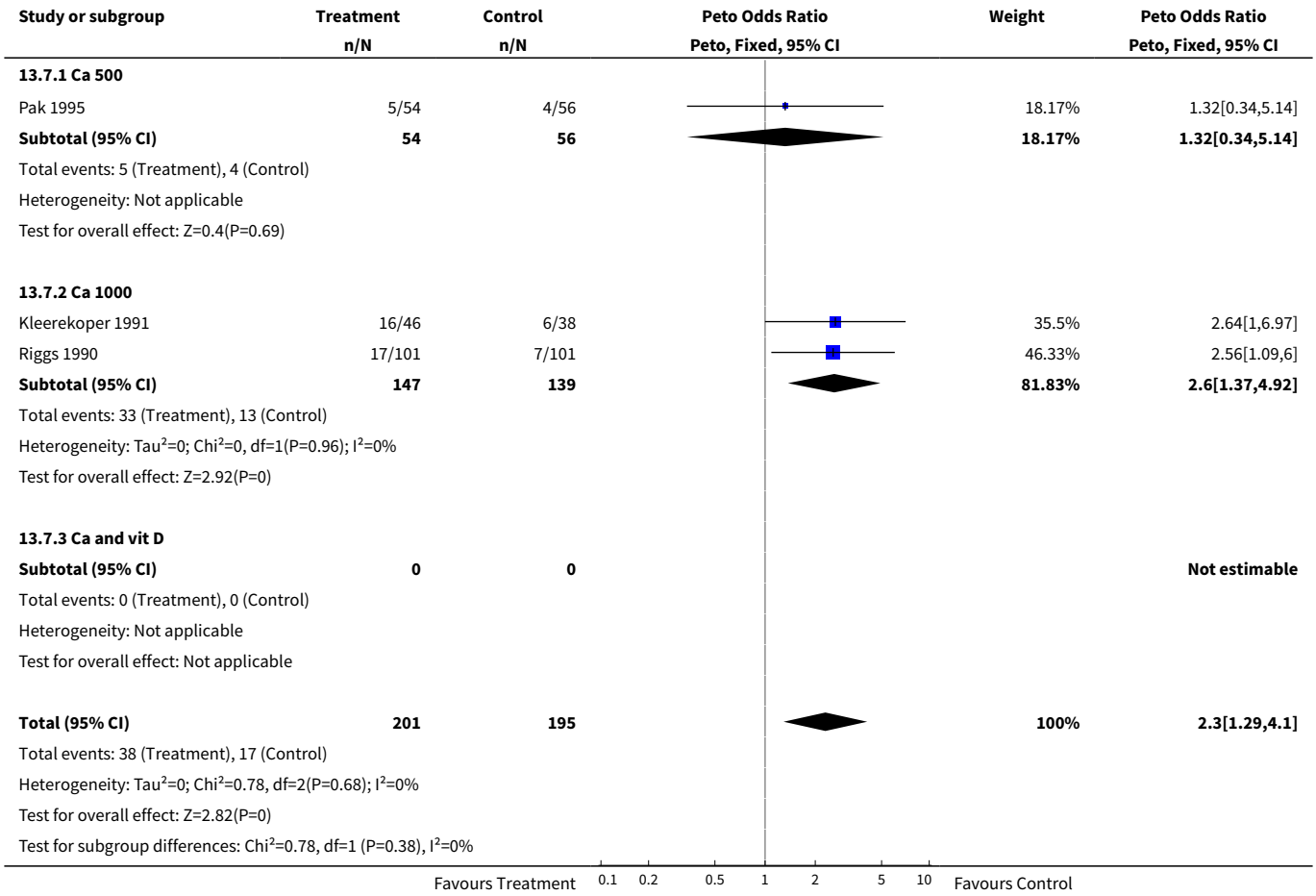


Analysis 13.6. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 6 GI minor 2 years.



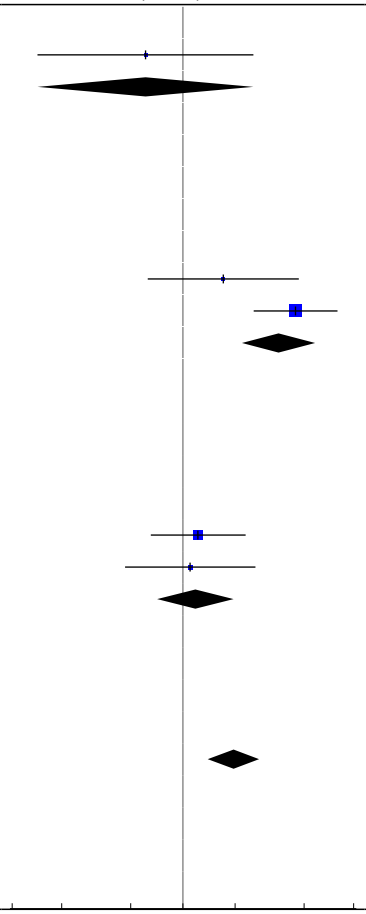


Analysis 13.7. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 7 GI minor 4 years.



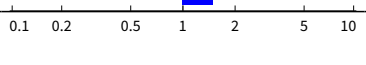
Analysis 13.8. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 8 Non vertebral fractures overall.

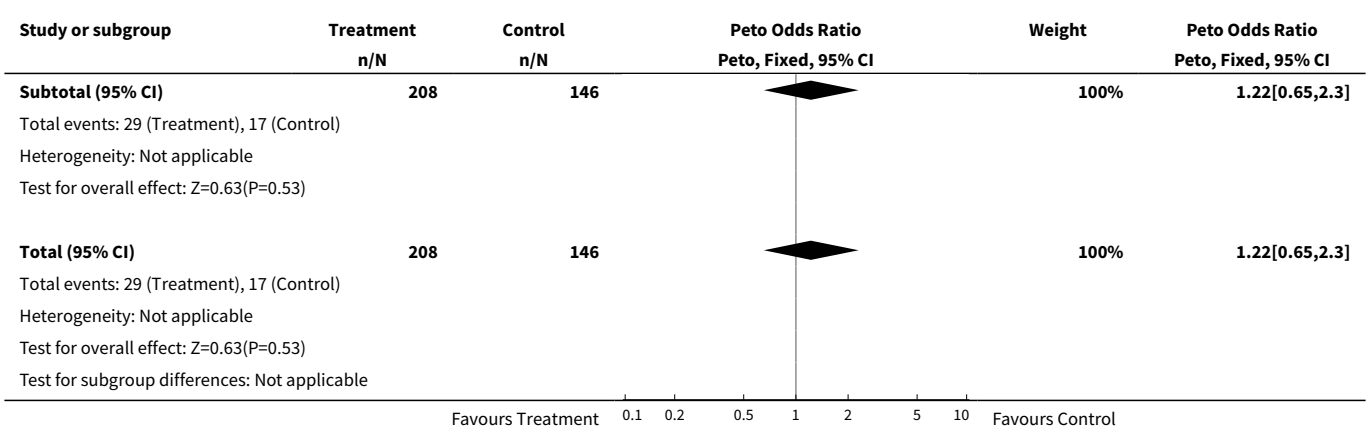
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
13.8.1 Ca 500					
Pak 1995	3/54	5/56		5.69%	0.61[0.15,2.55]
Subtotal (95% CI)	**54**	**56**		**5.69%**	**0.61[0.15,2.55]**
Total events: 3 (Treatment), 5 (Control)					
Heterogeneity: 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		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 (Control)					
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)					
13.8.3 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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**509**	**441**		**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=12.12, df=1 (P=0), I^2=83.49%					



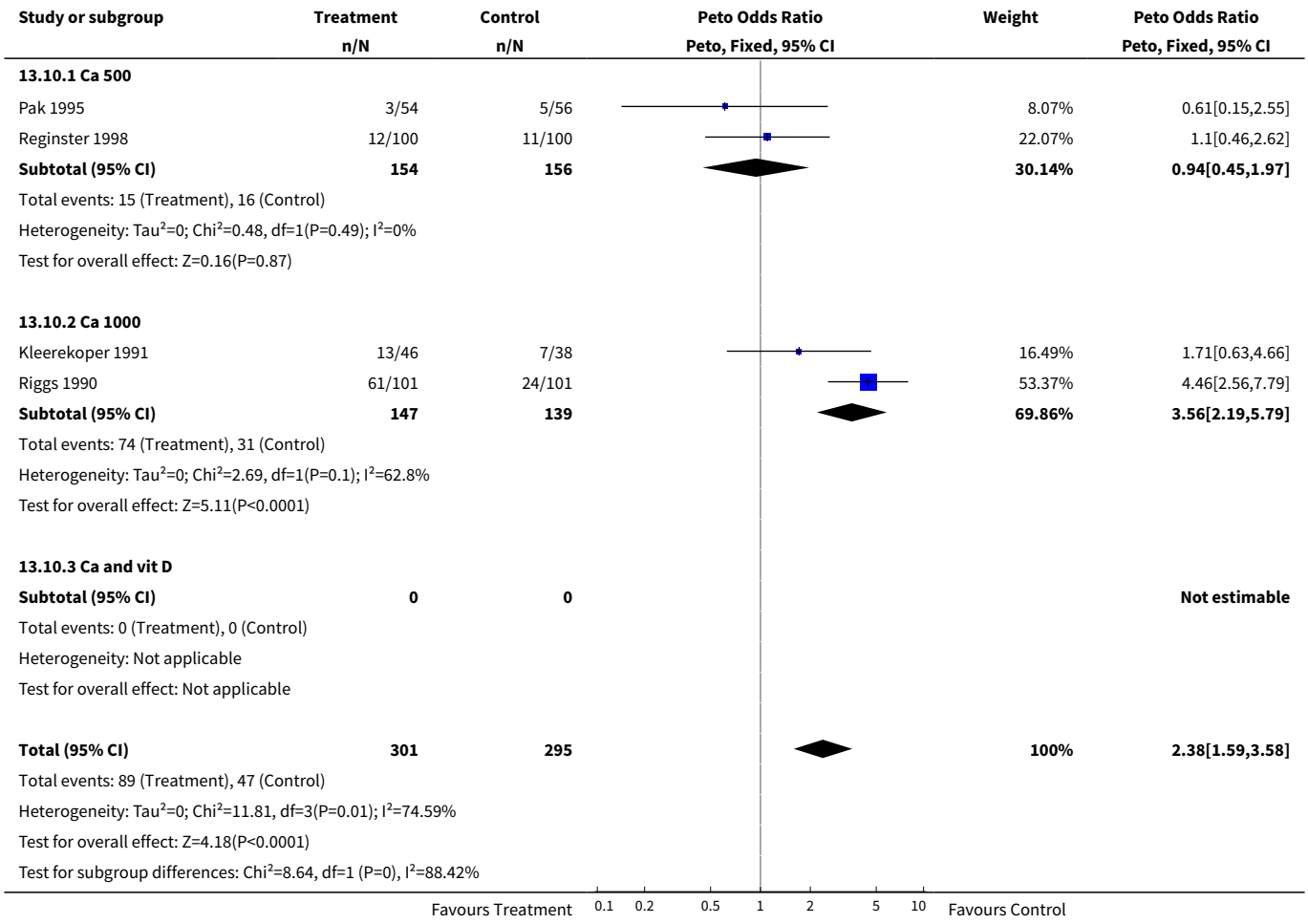
Analysis 13.9. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 9 Non vertebral fractures 2 years.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio 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]

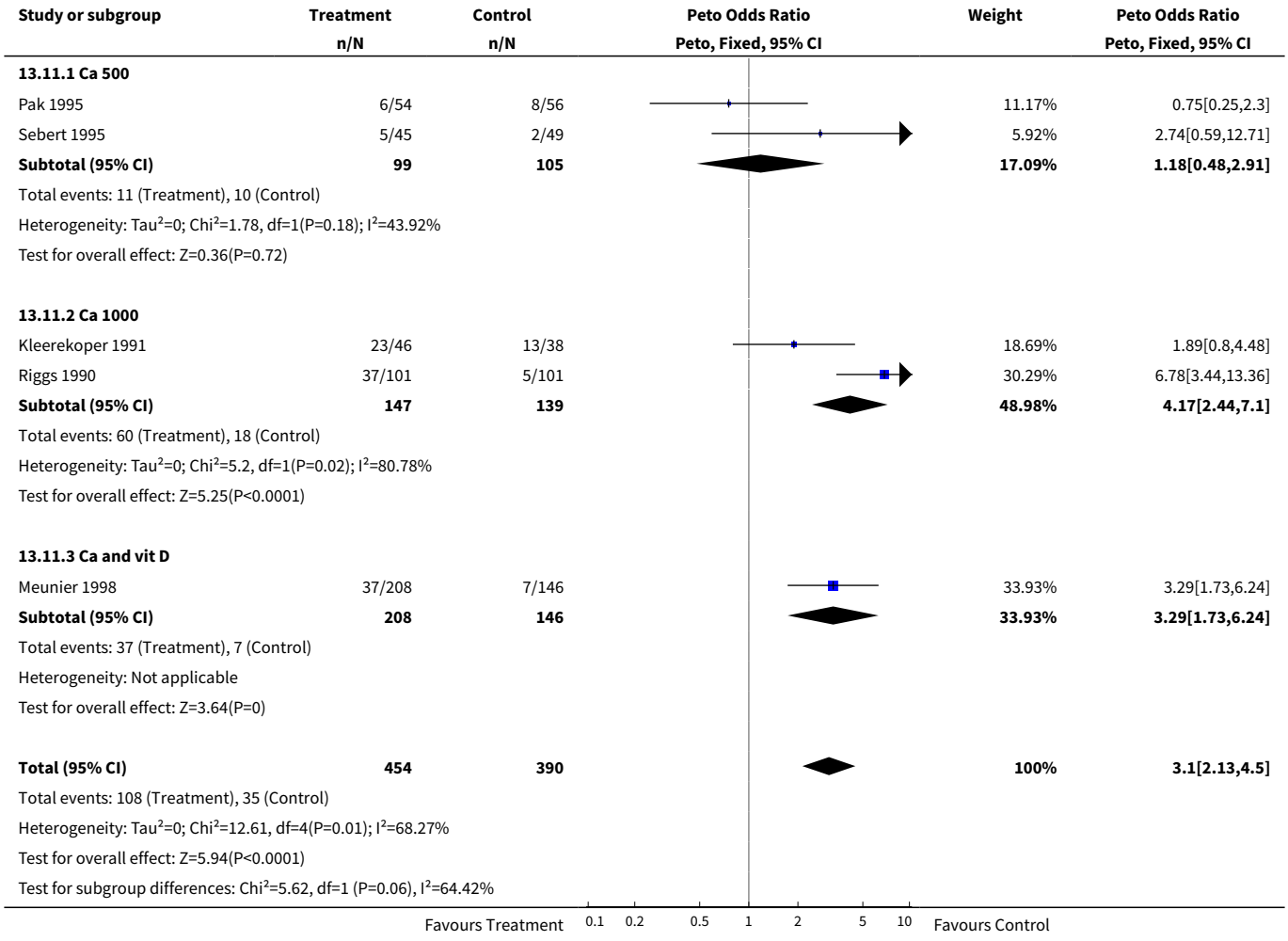




Analysis 13.10. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 10 Non vertebral fractures 4 years.

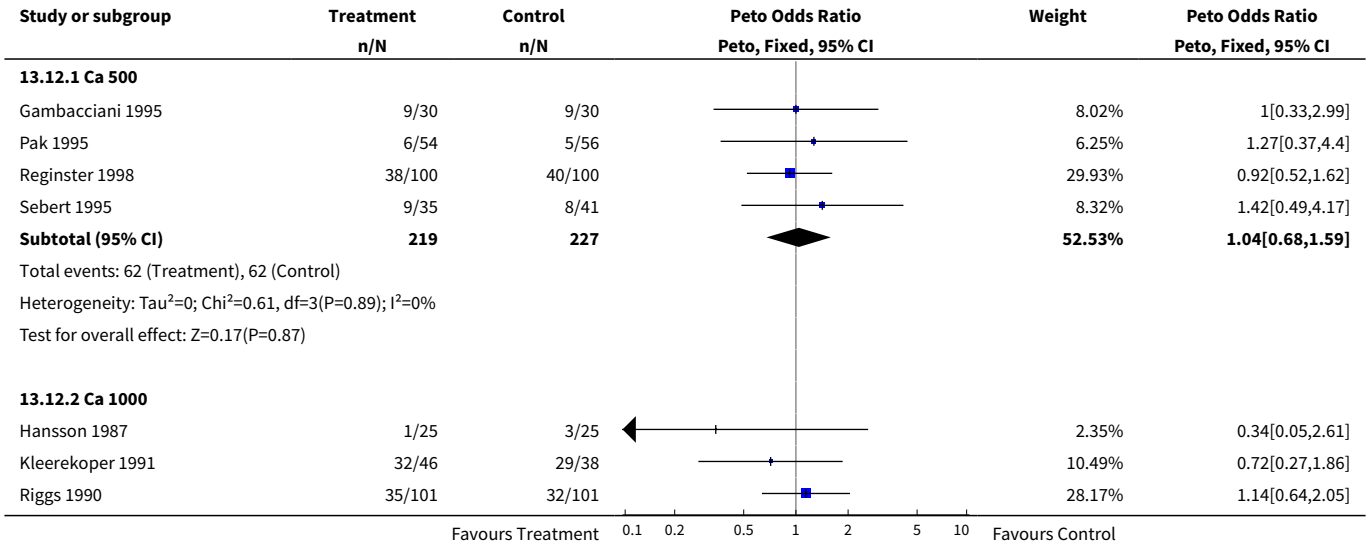


Analysis 13.11. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 11 Lower limb pain syndrome.

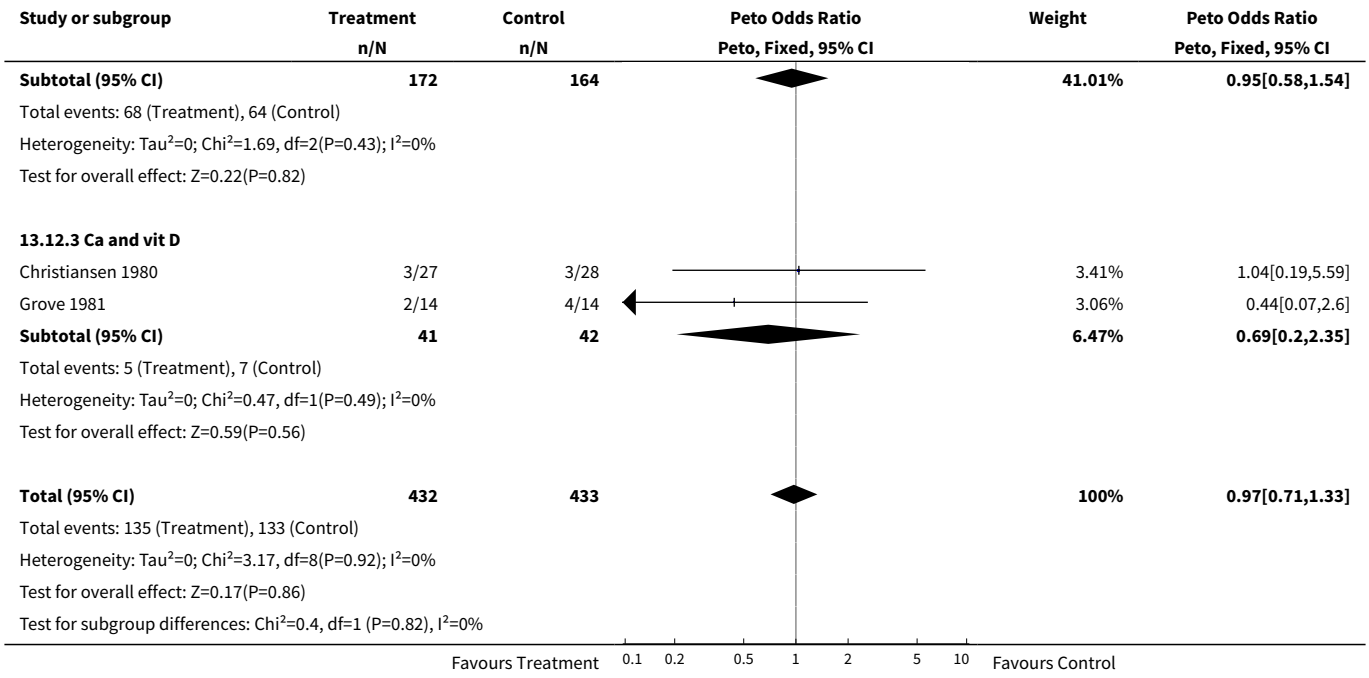


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
13.11.1 Ca 500					
Pak 1995	6/54	8/56		11.17%	0.75[0.25,2.3]
Sebert 1995	5/45	2/49		5.92%	2.74[0.59,12.71]
Subtotal (95% CI)	**99**	**105**		**17.09%**	**1.18[0.48,2.91]**
Total events: 11 (Treatment), 10 (Control)					
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 (Control)					
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)					
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 (Control)					
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 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.61, df=4(P=0.01); I^2=68.27%					
Test for overall effect: Z=5.94(P<0.0001)					
Test for subgroup differences: Chi^2=5.62, df=1 (P=0.06), I^2=64.42%					

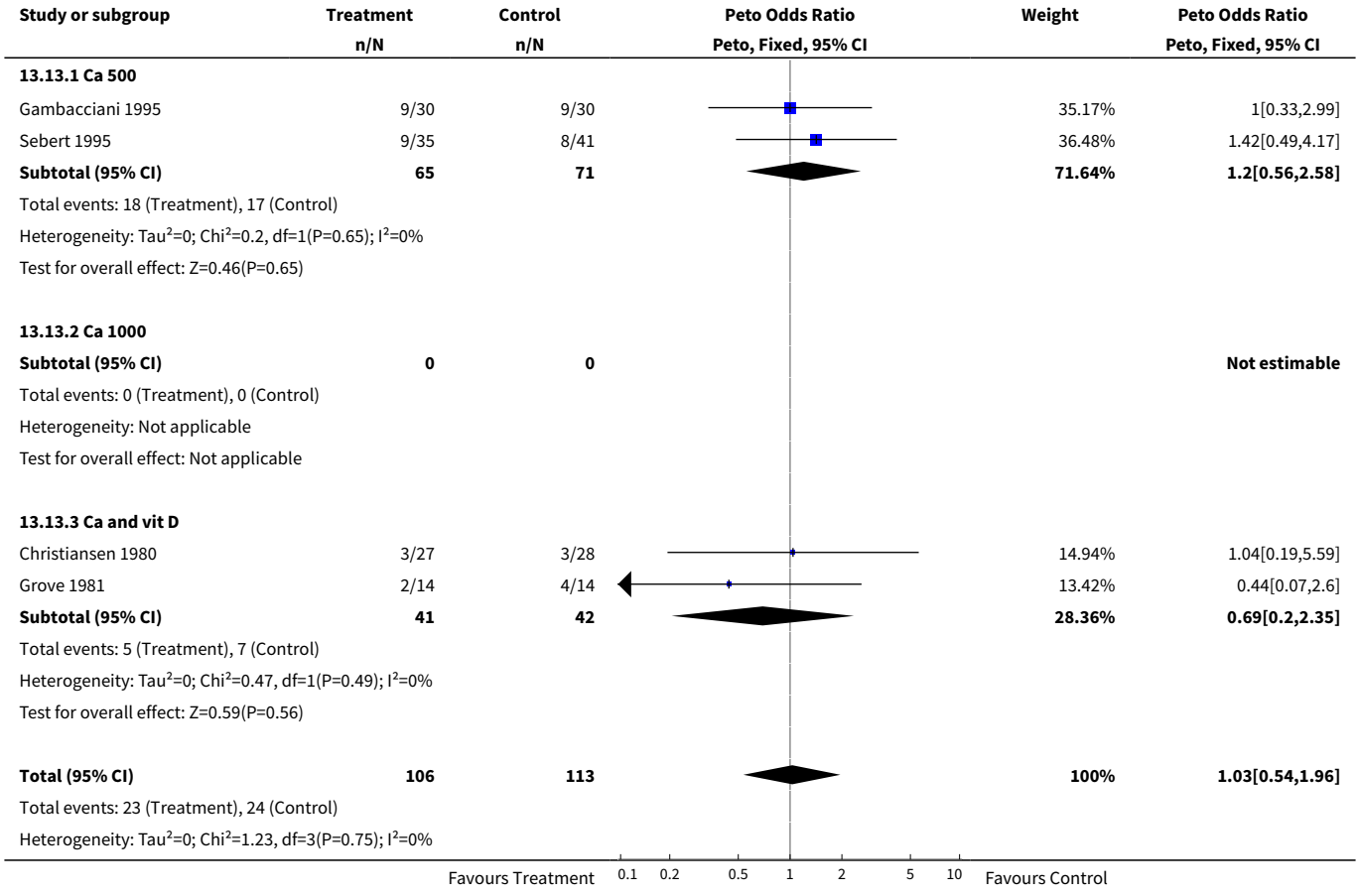
Analysis 13.12. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 12 Withdrawals and dropouts overall.

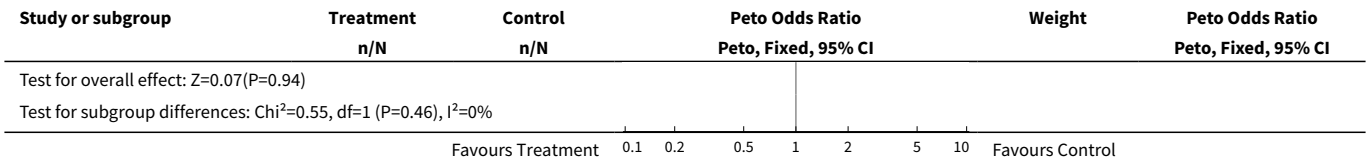


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
13.12.1 Ca 500					
Gambacciani 1995	9/30	9/30		8.02%	1[0.33,2.99]
Pak 1995	6/54	5/56		6.25%	1.27[0.37,4.4]
Reginster 1998	38/100	40/100		29.93%	0.92[0.52,1.62]
Sebert 1995	9/35	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 (Control)					
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]

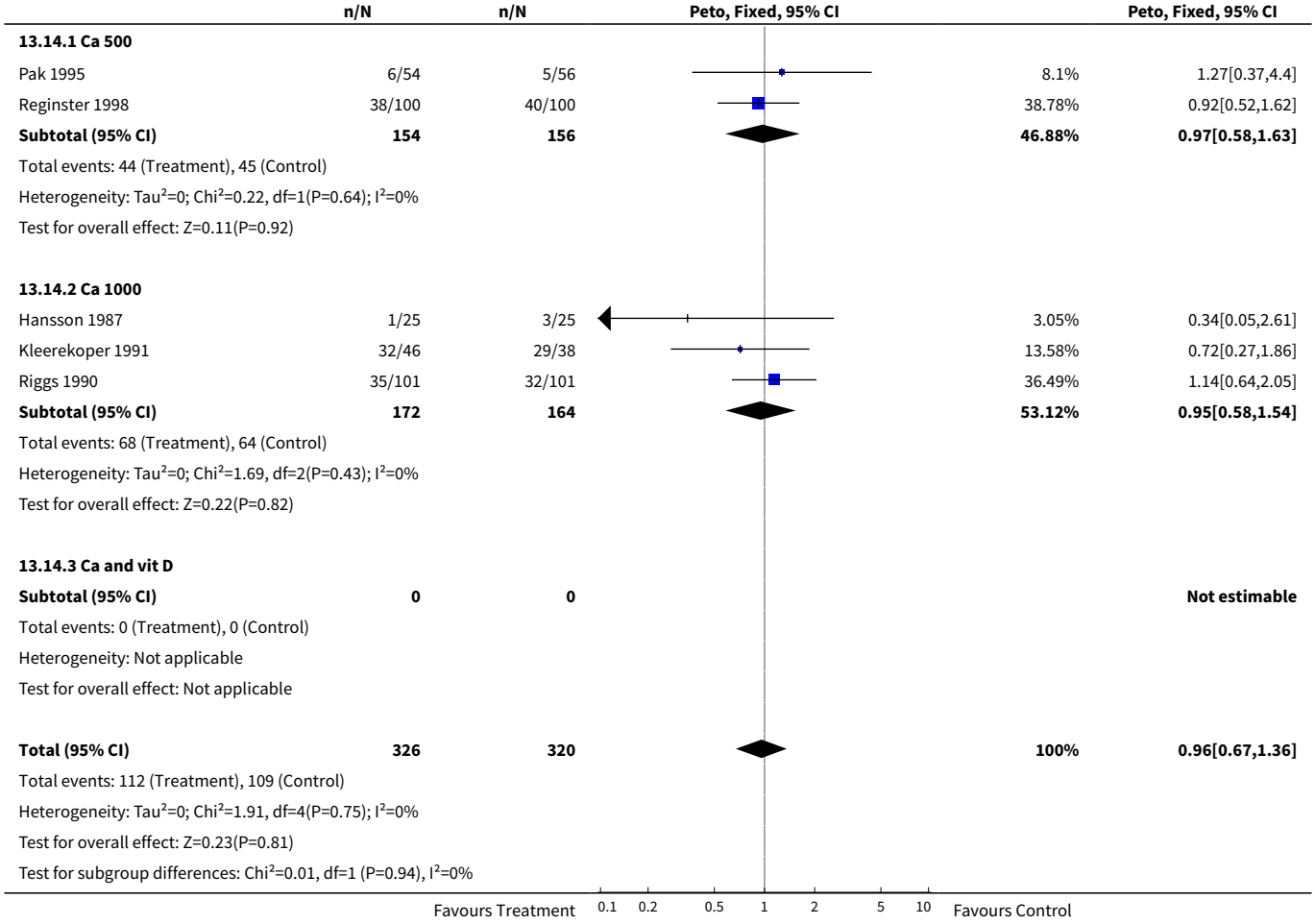


Analysis 13.13. Comparison 13 Subgroup Ca dosage and/or vit D, Outcome 13 Withdrawals and dropouts 2 years.





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



Comparison 14. Subgroup Osteoporosis definition

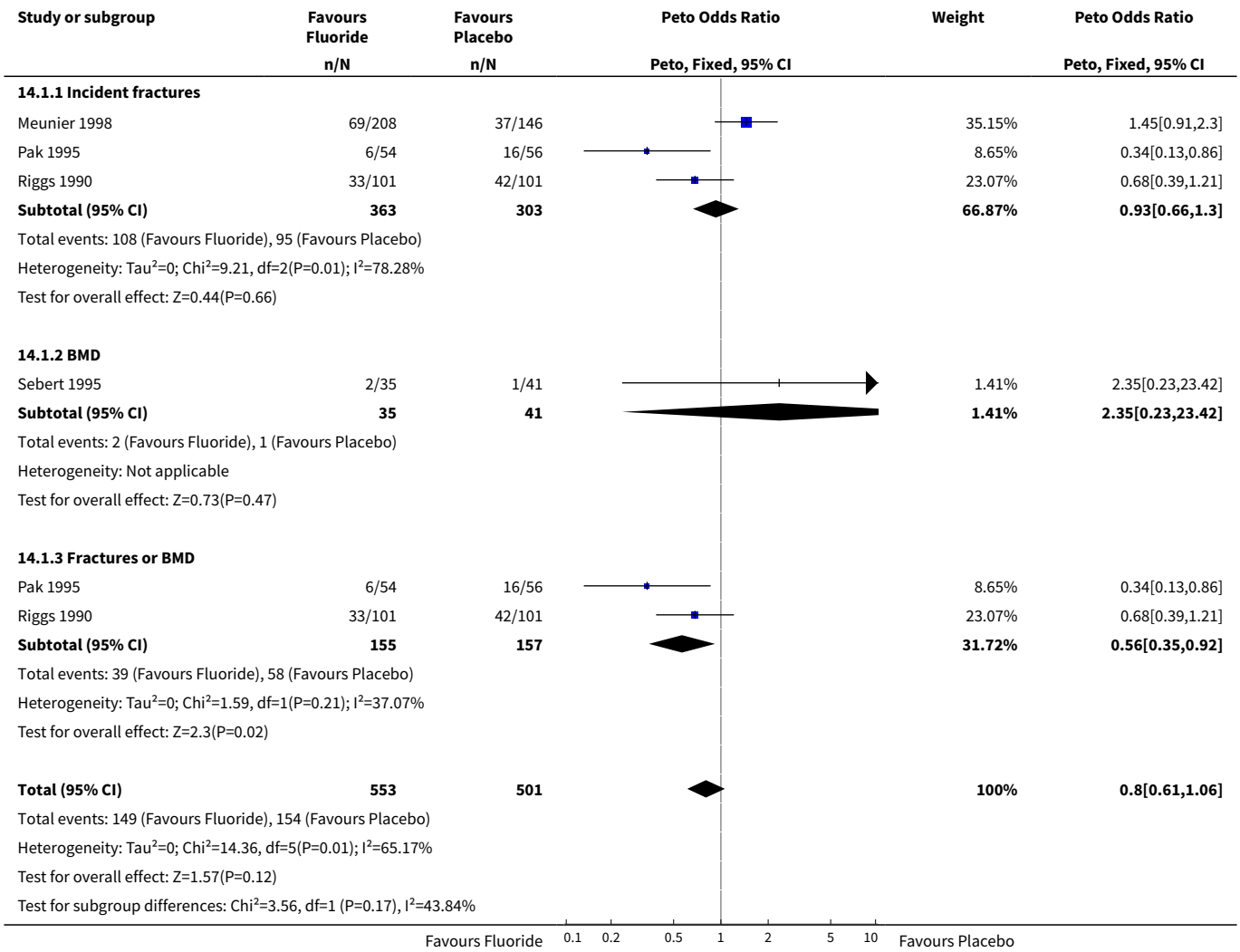
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. People with new vertebral fractures - 2 years	4	1054	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.61, 1.06]
1.1 Incident fractures	3	666	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.66, 1.30]

Outcome or subgroup title	No. of studies	No. of participants	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]

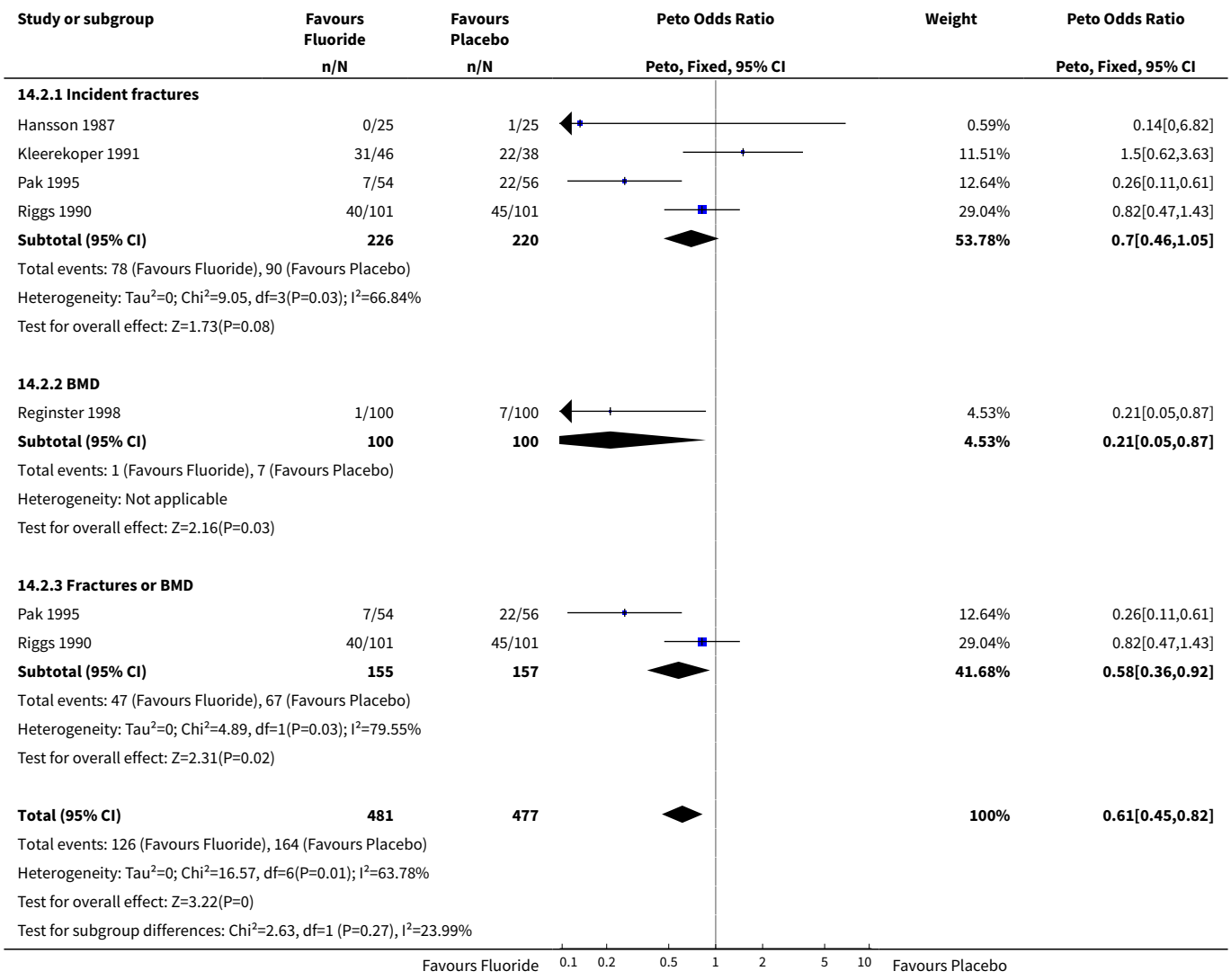
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 Fractures or BMD	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.43 [1.82, 6.45]
8 Non vertebral fractures overall	5	1262	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [1.74, 3.09]
8.1 Incident fractures	4	750	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 fractures 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 fractures 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 syndrome	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]

Outcome or subgroup title	No. of studies	No. of participants	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]

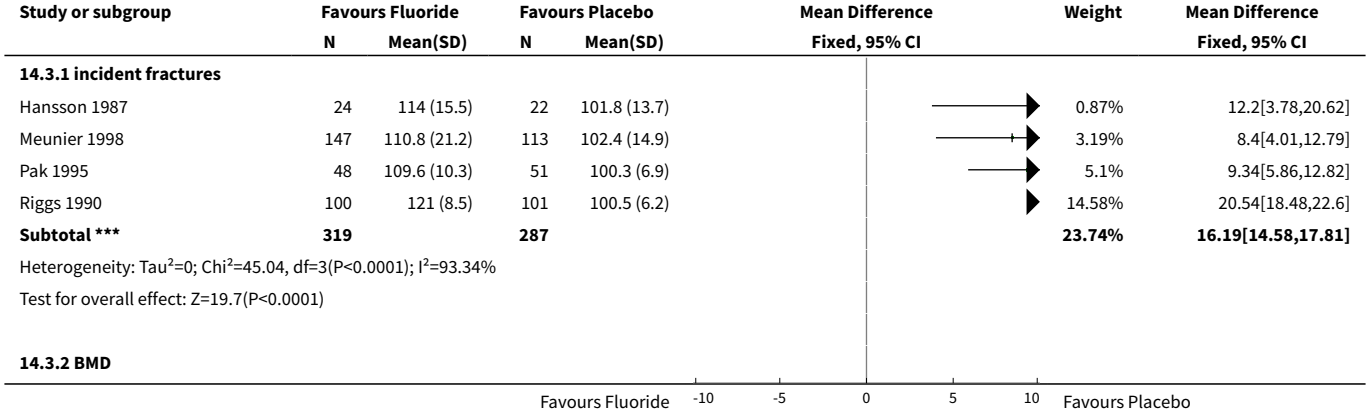
Analysis 14.1. Comparison 14 Subgroup Osteoporosis definition, Outcome 1 No. People with new vertebral fractures - 2 years.

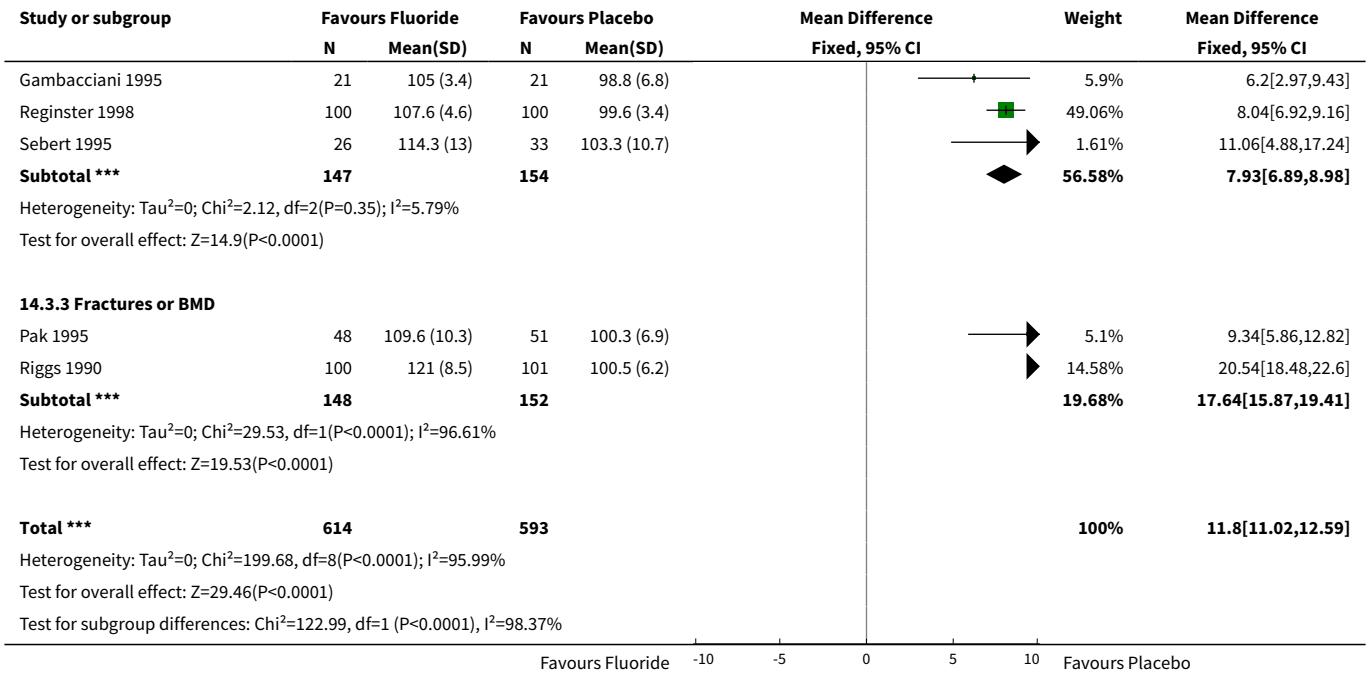


Analysis 14.2. Comparison 14 Subgroup Osteoporosis definition, Outcome 2 No. People with new vertebral fractures - 4 years.

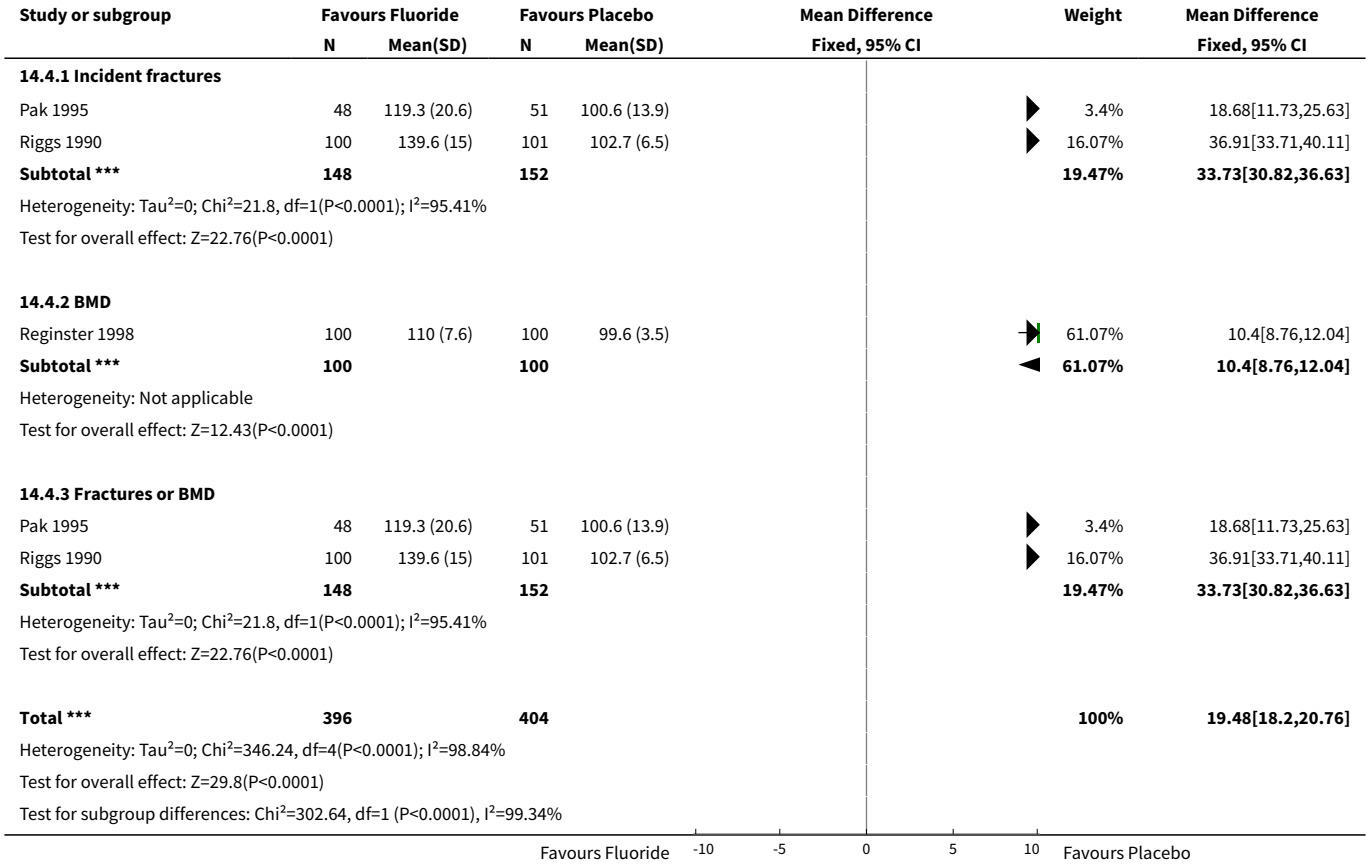


Analysis 14.3. Comparison 14 Subgroup Osteoporosis definition, Outcome 3 Lumbar BMD % from baseline 2 years.

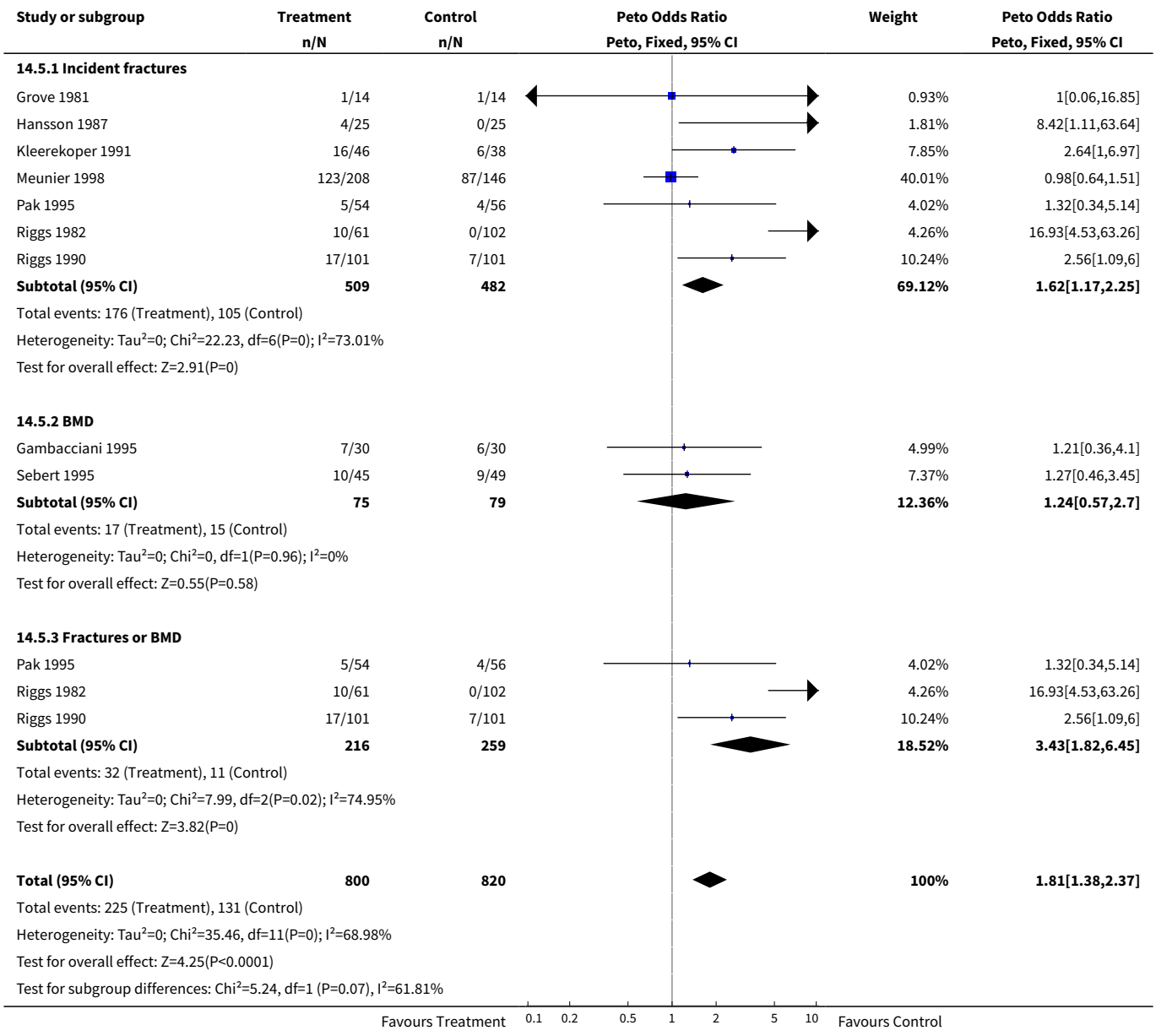




Analysis 14.4. Comparison 14 Subgroup Osteoporosis definition, Outcome 4 Lumbar BMD % from baseline 4 years.

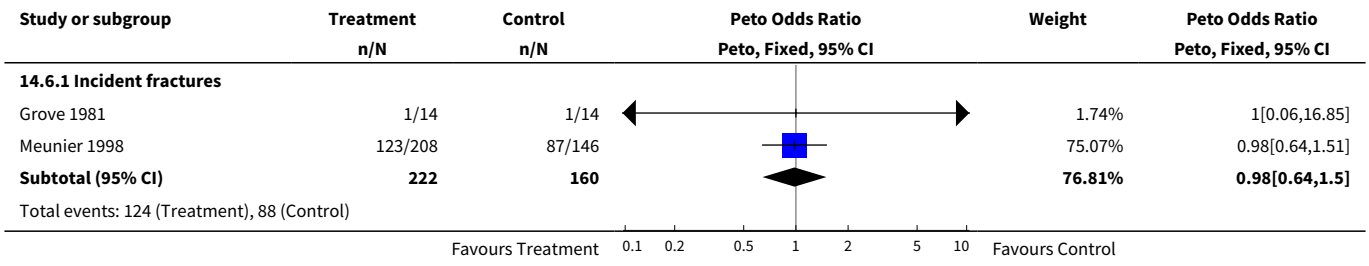


Analysis 14.5. Comparison 14 Subgroup Osteoporosis definition, Outcome 5 GI minor overall.

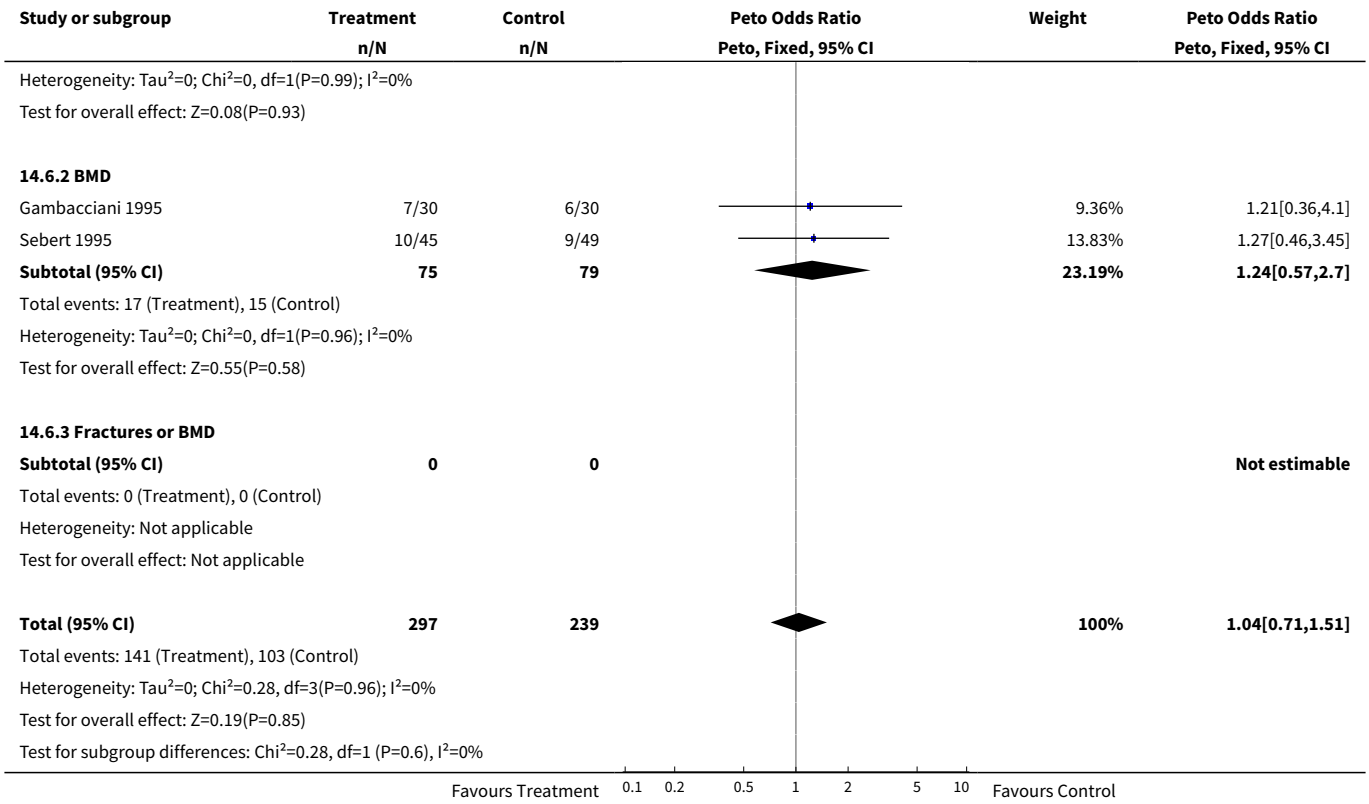


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
14.5.1 Incident fractures					
Grove 1981	1/14	1/14		0.93%	1[0.06,16.85]
Hansson 1987	4/25	0/25		1.81%	8.42[1.11,63.64]
Kleerekoper 1991	16/46	6/38		7.85%	2.64[1,6.97]
Meunier 1998	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 (Control)					
Heterogeneity: Tau²=0; Chi²=22.23, df=6(P=0); I²=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 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=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 1990	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 (Control)					
Heterogeneity: Tau²=0; Chi²=7.99, df=2(P=0.02); I²=74.95%					
Test for overall effect: Z=3.82(P=0)					
Total (95% CI)	**800**	**820**		**100%**	**1.81[1.38,2.37]**
Total events: 225 (Treatment), 131 (Control)					
Heterogeneity: Tau²=0; Chi²=35.46, df=11(P=0); I²=68.98%					
Test for overall effect: Z=4.25(P<0.0001)					
Test for subgroup differences: Chi²=5.24, df=1 (P=0.07), I²=61.81%					

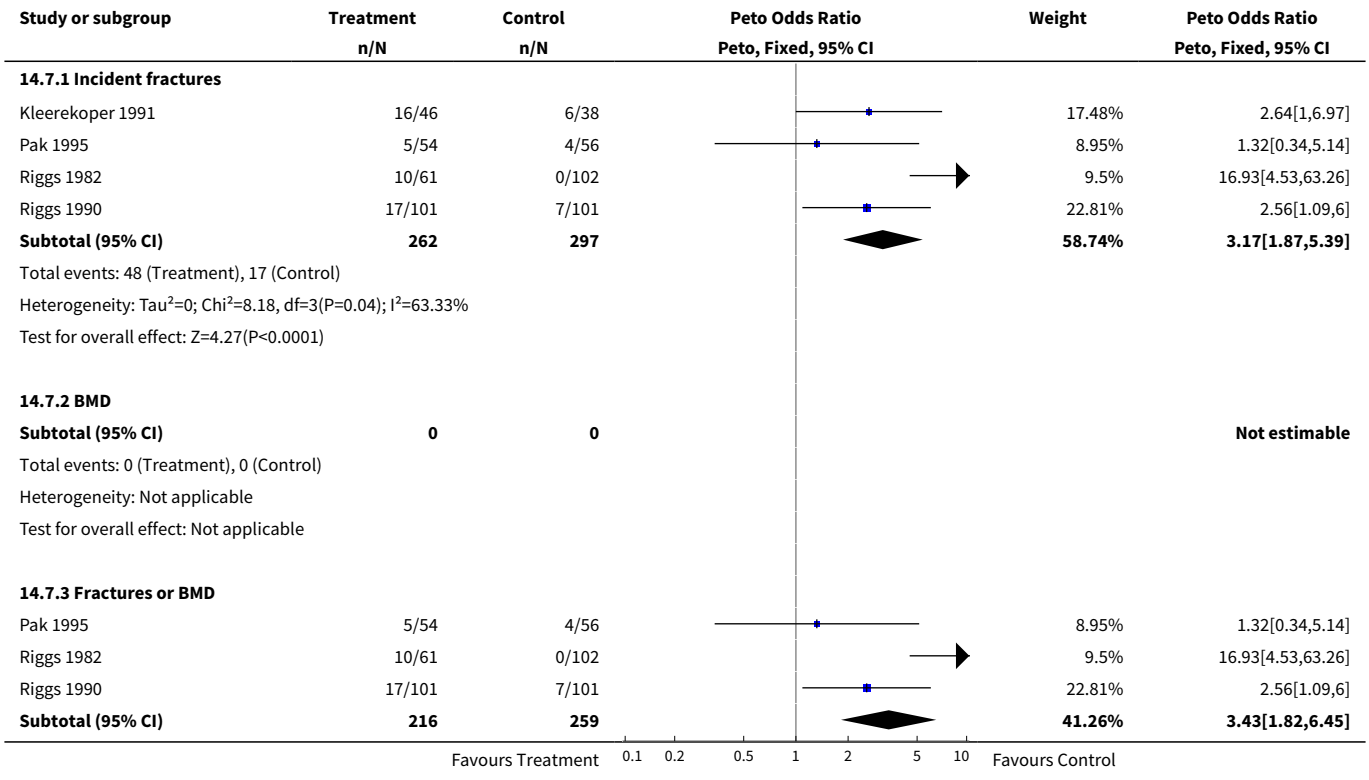
Analysis 14.6. Comparison 14 Subgroup Osteoporosis definition, Outcome 6 GI minor 2 years.

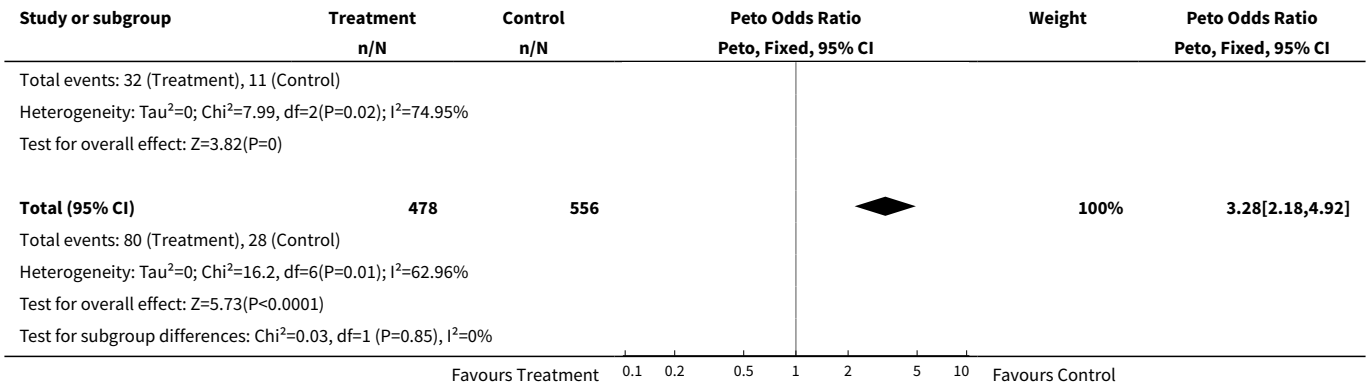


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
14.6.1 Incident fractures					
Grove 1981	1/14	1/14		1.74%	1[0.06,16.85]
Meunier 1998	123/208	87/146		75.07%	0.98[0.64,1.51]
Subtotal (95% CI)	**222**	**160**		**76.81%**	**0.98[0.64,1.5]**
Total events: 124 (Treatment), 88 (Control)					

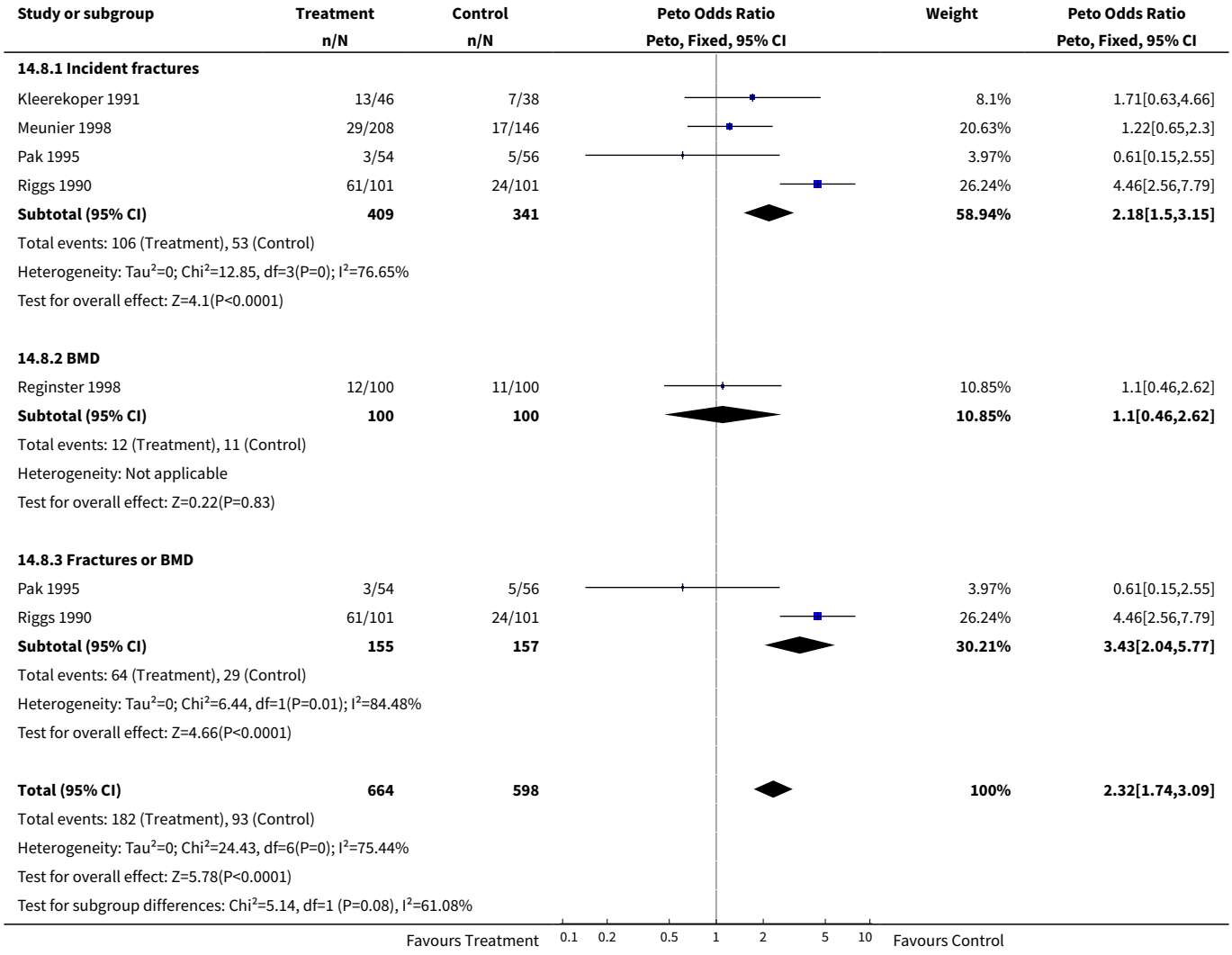


Analysis 14.7. Comparison 14 Subgroup Osteoporosis definition, Outcome 7 GI minor 4 years.





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

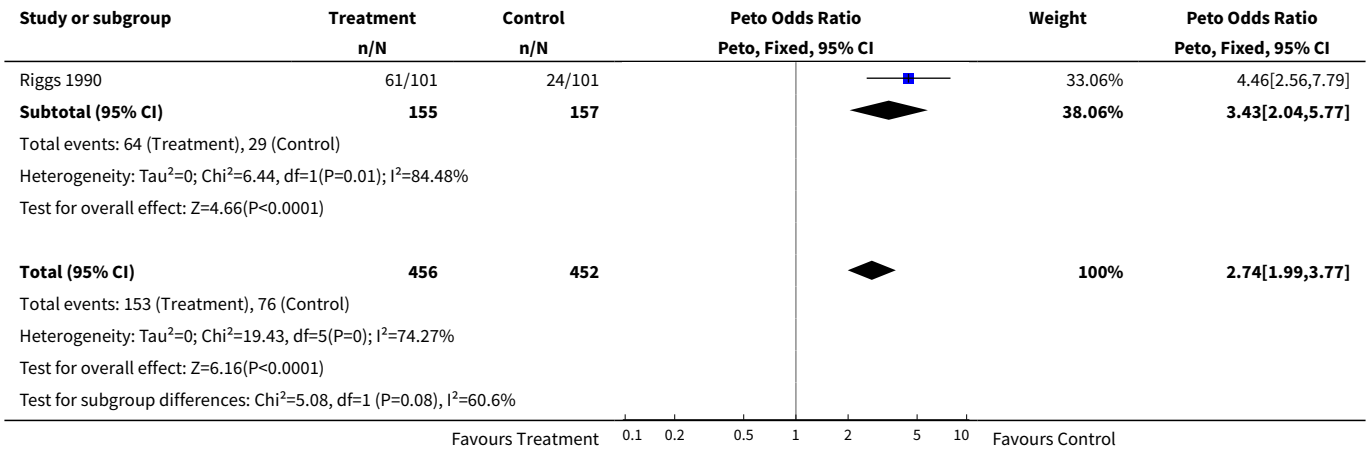


Analysis 14.9. Comparison 14 Subgroup Osteoporosis definition, Outcome 9 Non vertebral fractures 2 years.

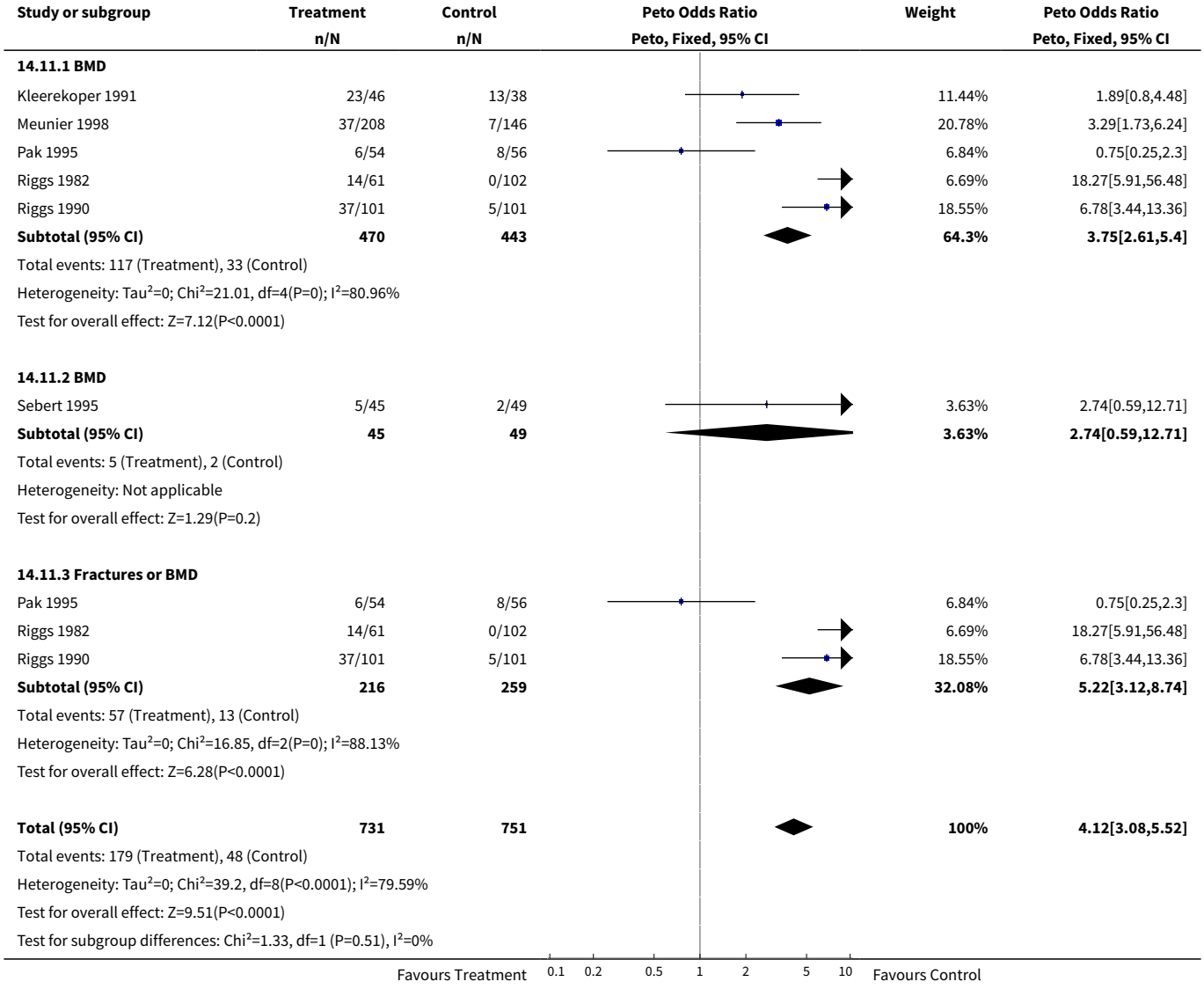
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
14.9.1 Incident fractures					
Meunier 1998	29/208	17/146		100%	1.22[0.65,2.3]
Subtotal (95% CI)	**208**	**146**		**100%**	**1.22[0.65,2.3]**
Total events: 29 (Treatment), 17 (Control)					
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 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not applicable					

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

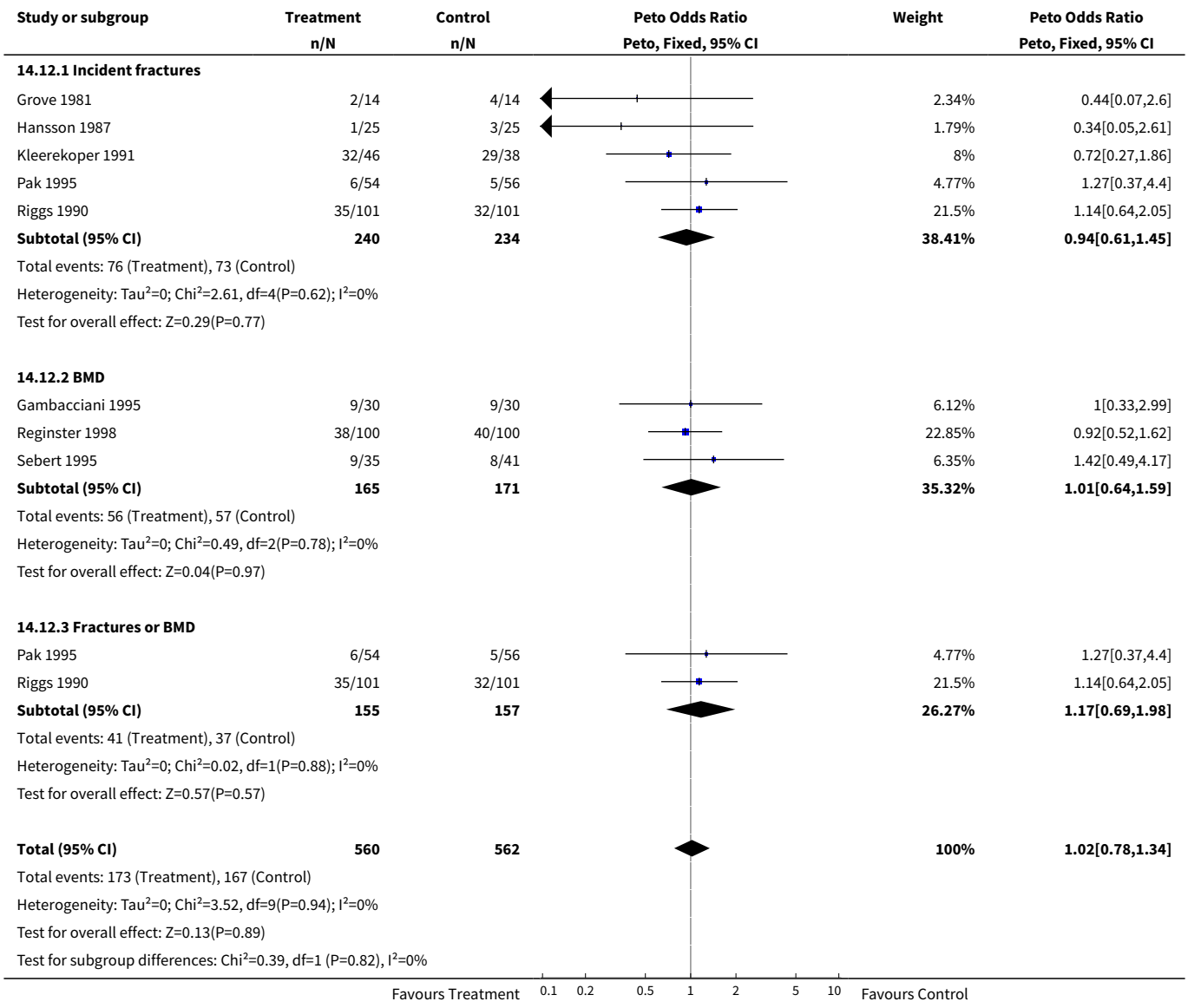
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
14.10.1 Incident fractures					
Kleerekoper 1991	13/46	7/38		10.21%	1.71[0.63,4.66]
Pak 1995	3/54	5/56		5%	0.61[0.15,2.55]
Riggs 1990	61/101	24/101		33.06%	4.46[2.56,7.79]
Subtotal (95% CI)	**201**	**195**		**48.27%**	**2.96[1.87,4.7]**
Total events: 77 (Treatment), 36 (Control)					
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<0.0001)					
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 (Control)					
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]



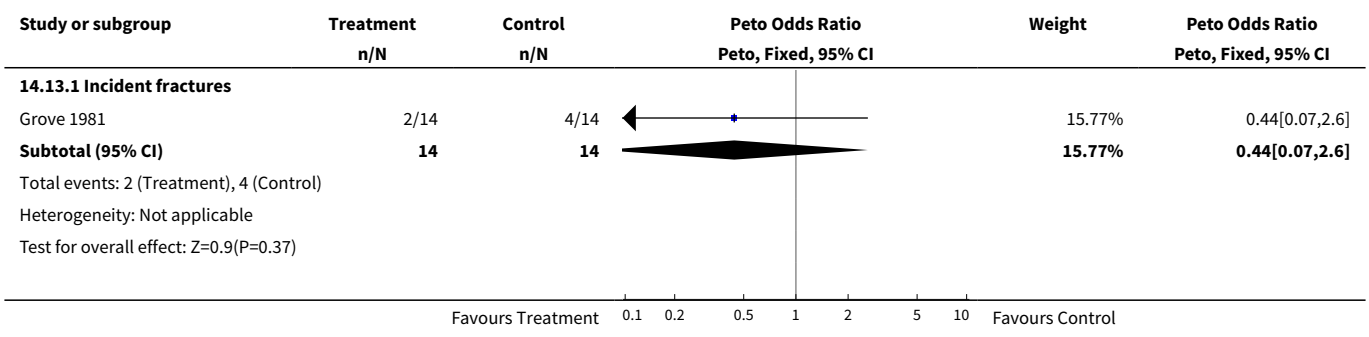
Analysis 14.11. Comparison 14 Subgroup Osteoporosis definition, Outcome 11 Lower limb pain syndrome.

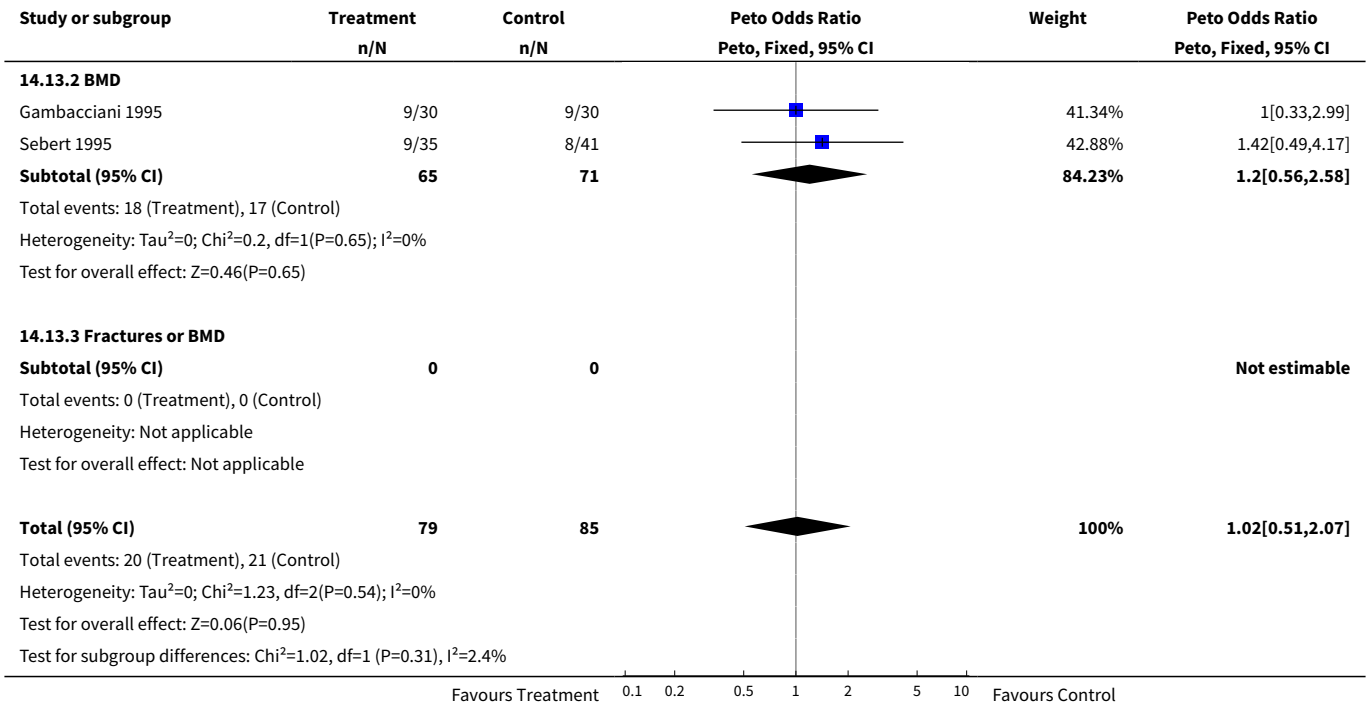


Analysis 14.12. Comparison 14 Subgroup Osteoporosis definition, Outcome 12 Withdrawals and dropouts overall.

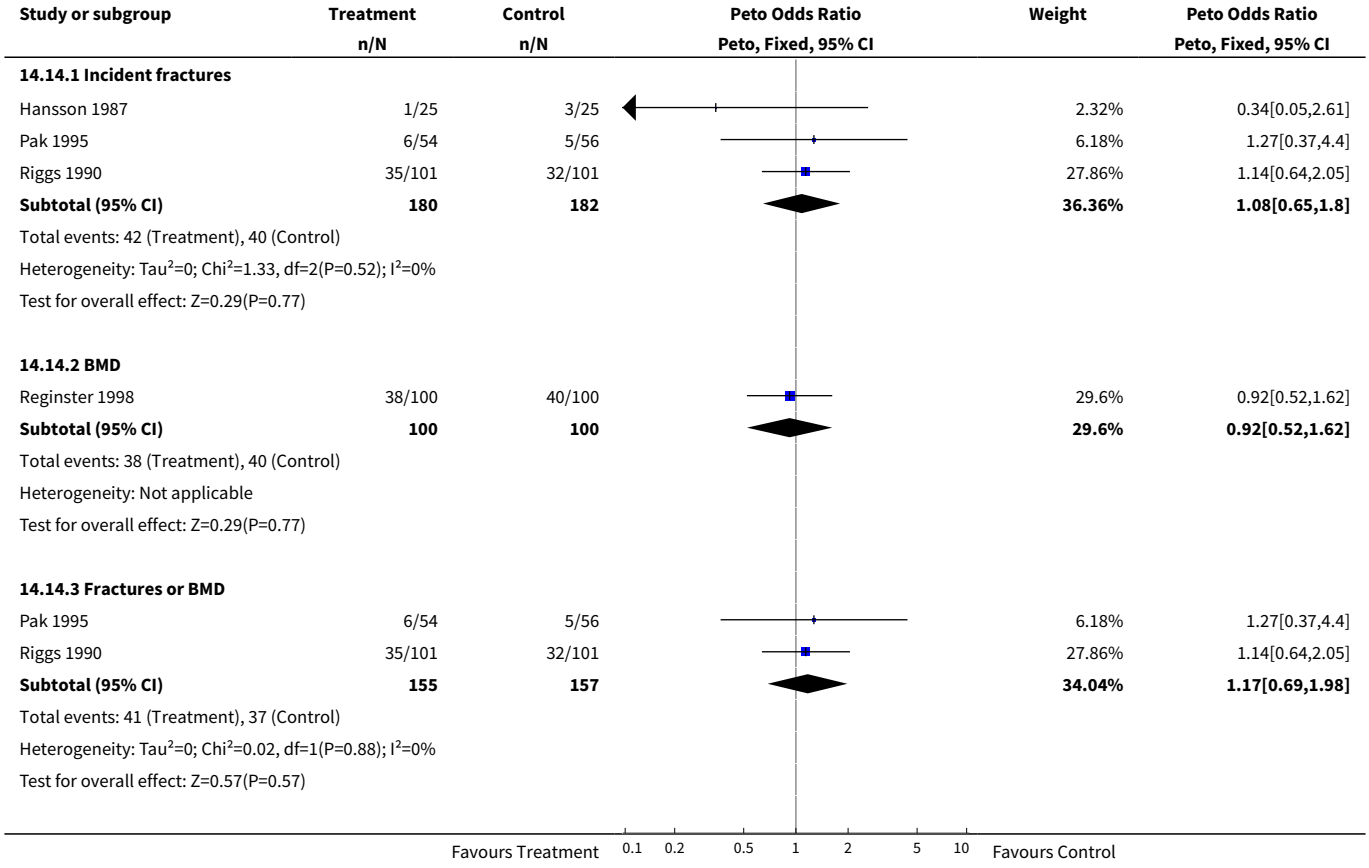


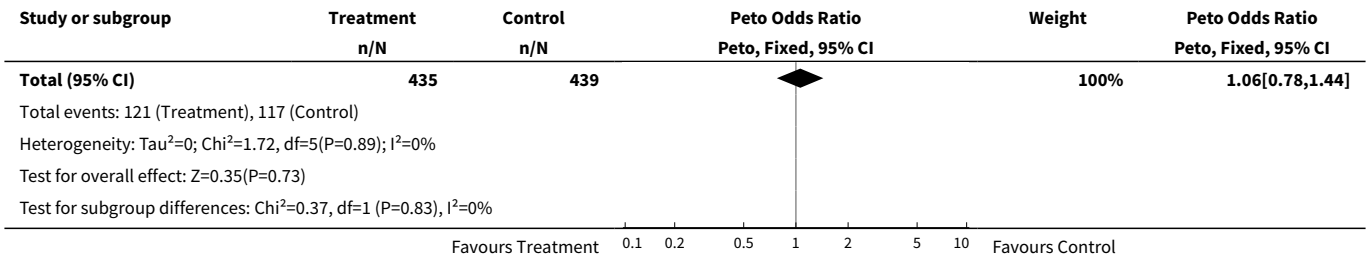
Analysis 14.13. Comparison 14 Subgroup Osteoporosis definition, Outcome 13 Withdrawals and dropouts 2 years.





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





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