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[Intervention Review]

Steroidal contraceptives: effect on bone fractures in women

Laureen M Lopez[1], David A Grimes[2], Kenneth F Schulz[3], Kathryn M. Curtis[4], Mario Chen[5]

[1]Clinical Sciences, FHI 360, Durham, North Carolina, USA. [2]Obstetrics and Gynecology, University of North Carolina, School of Medicine, Chapel Hill, North Carolina, USA. [3]Quantitative Sciences, FHI 360 and UNC School of Medicine, Durham, North Carolina, USA. [4]Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. [5]Division of Biostatistics, FHI 360, Durham, NC, North Carolina, USA

Contact: Laureen M Lopez, Clinical Sciences, FHI 360, 359 Blackwell St, Suite 200, Durham, North Carolina, 27701, USA. llopez@fhi360.org.

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ABSTRACT

Background

Steroidal contraceptive use has been associated with changes in bone mineral density in women. Whether such changes increase the risk of fractures later in life is not clear. Osteoporosis is a major public health concern. Age-related decline in bone mass increases the risk of fracture, especially of the spine, hip, and wrist. Concern about bone health influences the recommendation and use of these effective contraceptives globally.

Objectives

Our aim was to evaluate the effect of using hormonal contraceptives before menopause on the risk of fracture in women.

Search methods

Through April 2014, we searched for studies of fracture or bone health and hormonal contraceptives in MEDLINE, POPLINE, CENTRAL, EMBASE, and LILACS, as well as ClinicalTrials.gov and ICTRP. We examined reference lists of relevant articles for other trials. For the initial review, we wrote to investigators to find additional trials.

Selection criteria

Randomized controlled trials (RCTs) were considered if they examined fractures, bone mineral density (BMD), or bone turnover markers in women with hormonal contraceptive use prior to menopause. Eligible interventions included comparisons of a hormonal contraceptive with a placebo or with another hormonal contraceptive that differed in terms of drug, dosage, or regimen. They also included providing a supplement to one group.

Data collection and analysis

We assessed all titles and abstracts identified through the literature searches. Mean differences were computed using the inverse variance approach. For dichotomous outcomes, the Mantel-Haenszel odds ratio (OR) was calculated. Both included the 95% confidence interval (CI) and used a fixed-effect model. Due to differing interventions, no trials could be combined for meta-analysis. We applied principles from GRADE to assess the evidence quality and address confidence in the effect estimates. In addition, a sensitivity analysis included trials that provided sufficient data for this review and evidence of at least moderate quality.

Main results

We found 19 RCTs that met our eligibility criteria. Eleven trials compared different combined oral contraceptives (COCs) or regimens of COCs; five examined an injectable versus another injectable, implant, or IUD; two studied implants, and one compared the transdermal

patch versus the vaginal ring. No trial had fracture as an outcome. BMD was measured in 17 studies and 12 trials assessed biochemical markers of bone turnover. Depot medroxyprogesterone acetate (DMPA) was associated with decreased bone mineral density (BMD). The placebo-controlled trials showed BMD increases for DMPA plus estrogen supplement and decreases for DMPA plus placebo supplement. COCs did not appear to negatively affect BMD, and some formulations had more positive effects than others. However, no COC trial was placebo-controlled. Where studies showed differences between groups in bone turnover markers, the results were generally consistent with those for BMD. For implants, the single-rod etonogestrel group showed a greater BMD decrease versus the two-rod levonorgestrel group but results were not consistent across all implant comparisons.

The sensitivity analysis included 11 trials providing evidence of moderate or high quality. Four trials involving DMPA showed some positive effects of an estrogen supplement on BMD, a negative effect of DMPA-subcutaneous on lumbar spine BMD, and a negative effect of DMPA on a bone formation marker. Of the three COC trials, one had a BMD decrease for the group with gestodene plus EE 15 µg. Another indicated less bone resorption in the group with gestodene plus EE 30 µg versus EE 20 µg.

Authors' conclusions

Whether steroidal contraceptives influence fracture risk cannot be determined from existing information. The evidence quality was considered moderate overall, largely due to the trials of DMPA, implants, and the patch versus ring. The COC evidence varied in quality but was low overall. Many trials had small numbers of participants and some had large losses. Health care providers and women should consider the costs and benefits of these effective contraceptives. For example, injectable contraceptives and implants provide effective, long-term birth control yet do not involve a daily regimen. Progestin-only contraceptives are considered appropriate for women who should avoid estrogen due to medical conditions.

PLAIN LANGUAGE SUMMARY

Hormonal contraceptives and bone health in women

Hormonal contraceptives have been related to bone changes in women. Whether such changes lead to more bone fractures later in life is not clear. However, bone health is a major public health concern. Bone density declines with age, and the change increases the risk of fracture. Due to concern about bone health, health care providers may not suggest hormonal contraceptives and women may not want to use them.

Through April 2014, we did computer searches for studies of birth control methods containing hormones and risk of fractures. Outcomes could also be bone mineral density or markers of bone changes. Birth control pills included types with both estrogen and progestin. Also included were implants and injectables with only progestin. We wrote to researchers to find other trials. We included randomized trials in any language that had at least three treatment cycles. The studies had to compare two types of birth control or one type of birth control or a supplement with a placebo or 'dummy' method.

We found 19 trials. Fifteen studies compared one birth control method with another hormone method. Two trials used a placebo or 'dummy.' One compared a hormone method to a method without hormones. None had fractures as an outcome and most looked at bone density. Birth control methods with both estrogen and progestin did not appear to affect bone health. However, 'depo,' which is injected and has only progestin, was related to lower bone density. The two depo trials with placebos showed increased bone density when some estrogen was given to women on depo. Bone density decreased in women who got a 'dummy' with the depo. Whether this decrease is important to the woman's health is not known. For implants, an etonogestrel implant with one rod showed a greater decrease in bone density than a two-rod levonorgestrel implant. However, other implants studied did not show the same pattern.

The studies had data of moderate quality. Whether hormonal contraceptives affect fracture risk cannot be judged from current information. These contraceptive methods work well for birth control. Health-care providers and women should think about the costs and benefits. For instance, injectable use can occur without a partner's knowledge, and is simpler than taking pills every day. Also, progestin-only methods are suggested for some women with health problems who should avoid estrogen.

BACKGROUND

Description of the condition

Steroidal contraceptives, particularly injectable contraceptives and combined oral contraceptives (COCs), have been associated with changes in bone mineral density in women. Whether such changes increase the risk of fractures later in life is not clear. However, osteoporosis is a major public health concern. Age-related decline in bone mass increases the risk of fracture, especially of the spine, hip, and wrist (Howe 2011; Rachner 2011). The costs of osteoporosis-related fractures can be substantial for the individual due to disability and to society for health and social care (Howe 2011). Concern about bone health influences the recommendation and use of these effective contraceptives globally.

Skeletal fragility results from suboptimal formation of bone mass and strength, as well as excess bone resorption (NIH 2000; Raisz 2005). Bone loss during contraceptive use may be temporary like that which occurs during pregnancy or breastfeeding (Gourlay 2004; ACOG 2008). Risk of future fractures after contraceptive use depends on whether the bone mass is restored.

Description of the intervention

Depot medroxyprogesterone acetate (DMPA)

DMPA is an effective contraceptive and the most widely-used injectable (Bartz 2011). Data from developing countries showed median failure rates of 2.4% for injectables versus 10.3% for condoms and 6.5% for pills (Cleland 2004). First-year failure rates for DMPA in the USA have been estimated at 0.2% for perfect use and 6% for typical use (Trussell 2011). If injectable use were limited due to concerns about effects on bone health, women might switch to less effective methods or use nothing, which could lead to increased pregnancy rates.

Of the injectable contraceptives, DMPA has attracted the most attention regarding bone health. DMPA may reduce bone mineral density (BMD), which is a potential concern for younger women who have not yet achieved peak bone mass. Early research indicated more bone loss among women who used DMPA before 20 years of age and those who used it for longer periods (Cundy 1998; Scholes 1999). More recently, two case-control studies reported increased fracture risk for longer current use of DMPA (Vestergaard 2006; Meier 2010), although past users had little evidence of increased risk (Meier 2010).

In the US, the Food and Drug Administration requires a warning on DMPA labeling (FDA 2004; FDA 2011). It refers to BMD loss among DMPA users, especially younger women. The warning is based on limited evidence and may limit long-term use (Kaunitz 2011). Major health organizations have recommended not restricting DMPA use among women 18 to 45 years old (WHO 2006; ACOG 2008; Guilbert 2009). In guidance about medical eligibility criteria for contraceptive use, DMPA is category 1 (no restriction) for women aged 18 to 45 years (CDC 2010; WHO 2009). For women outside that age range, DMPA is category 2, meaning the advantages generally outweigh the theoretical or proven risks.

Oral contraceptives (OCs)

OCs are the most commonly used reversible method in more developed countries (UN 2011). Failure rates for oral contraceptives in the USA (combined and progestin-only) are estimated at 0.3% for perfect use and 9% for typical use in the first year (Trussell 2011).

Few associations have been noted between OC use and fracture risk in observational studies (Lopez 2012). A cohort study found OC ever-users had increased risk for all fractures (Cooper 1993). However, a case-control study, with later data from a subset, reported no association except for those with 10 years or more since use (Memon 2011). Another case-control study reported increased risk, but only for those who had 10 or more prescriptions (Meier 2010). A cohort study of postmenopausal women found no increased fracture risk for OC use after excluding women with prior fracture (Barad 2005). Two other studies found little evidence of association between OC use and fracture risk. A cohort study noted increased risk for subgroups, such as those with longer use or specific intervals since use (Vessey 1998). A case-control study reported increased risk for any fracture only among young women with less than average use (Vestergaard 2006).

COCs may have little effect on BMD among healthy adult women. Prospective studies have indicated that ultra-low dose COCs, containing 20 µg ethinyl estradiol, may affect bone development in young women (Cromer 2003). On the other hand, COCs with 30 to 40 µg ethinyl estradiol may have no negative effect and may even protect against bone loss, at least among women 30 years of age or more (Cromer 2003). Evidence from studies of varying designs indicates that BMD may be affected by COC use in adolescent and young women but not in adult premenopausal or postmenopausal women (Martins 2006; Herrmann 2010; Warholm 2012). However, COC use may have a negative effect on bone turnover markers, although the clinical significance of such change is unclear (Herrmann 2010).

Intrauterine device (IUD) or system (IUS)

For the levonorgestrel IUS, no mechanism is apparent that might affect bone health (Mansour 2012). However, a case-control study reported reduced fracture risk for ever-use of the hormonal IUD and longer use of that IUD (Vestergaard 2006).

Why it is important to do this review

Hormonal contraceptives are among the most effective and most widely-used contraceptives. Concern about fractures may limit the use of these effective contraceptives. Women might switch to less effective methods or use nothing, potentially leading to increased rates of unintended pregnancy. The question about an association between steroidal contraceptives and fractures is important to examine systematically with the available evidence. Since our initial review in 2006, we also examined evidence of actual fracture risk in observational studies of hormonal contraceptives (Lopez 2012). In this update, we further examine the effect of using steroidal contraceptives before menopause on general bone health, based on evidence from randomized controlled trials.

OBJECTIVES

Our aim was to evaluate the effect of using hormonal contraceptives before menopause on the risk of fracture in women.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized controlled trials (RCTs) if they examined fractures, bone mineral density, or bone turnover in women who used hormonal contraceptives prior to menopause.

Studies were excluded if hormones were provided for treatment of a specific condition or if the study focused on women with a certain condition, such as endometriosis, polycystic ovary disease, or hirsutism. Also excluded were studies that provided hormone replacement therapy to postmenopausal women.

Types of participants

We included women in the identified trials who were randomly assigned to study groups.

Types of interventions

Interventions included comparisons of a hormonal contraceptive with a placebo or with another hormonal contraceptive that differed in terms of drug, dosage, or regimen. Interventions also included the provision of a supplement, for example, another hormone or a vitamin or mineral preparation, to one group.

We excluded interventions involving exercise, which appears to interact with hormonal contraceptives to affect bone health.

Types of outcome measures

Primary outcomes

The primary outcome was fractures occurring after baseline, particularly fractures of the spine, hip, and wrist.

Secondary outcomes

- Bone mineral density, which could have been measured, e.g., at the femur, lumbar spine or whole body;
- Biochemical markers of bone turnover (Vasikaran 2011a; Vasikaran 2011b), e.g.,
  - bone formation - serum osteocalcin, alkaline phosphatase, and type I procollagen;
  - bone resorption - serum calcium and C-telopeptide; urinary pyridinoline and N-telopeptides.

Search methods for identification of studies

Electronic searches

Through April 2014, we searched the computerized databases MEDLINE, POPLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and LILACS for studies of fracture or bone health and hormonal contraceptives. In addition, we searched for recent clinical trials through ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP). The strategies are given in Appendix 1. Previous search strategies can be found in Appendix 2.

Searching other resources

We examined reference lists of relevant articles for other trials. For the initial review, we wrote to known investigators for information about other published or unpublished trials not discovered in our search.

Data collection and analysis

Selection of studies

We assessed for inclusion all titles and abstracts identified during the literature searches with no language limitation.

Data extraction and management

Two authors independently abstracted the data. Data were entered into RevMan, and a second author verified accuracy. Any discrepancies were resolved by discussion.

Assessment of risk of bias in included studies

Studies were examined for methodological quality, according to the principles recommended in Higgins 2011. Factors considered were study design, method for generating the randomization sequence, allocation concealment, blinding, and losses to follow up and early discontinuation. We also examined the methods used for assessing the outcomes.

Assessment of heterogeneity

None of the trials examined the same types of interventions. Therefore, we did not combine any trials in a meta-analysis.

Data synthesis

For continuous variables, the mean difference (MD) was computed with 95% confidence interval (CI) using a fixed-effect model. RevMan uses the inverse variance approach. For dichotomous outcomes, the Mantel-Haenszel odds ratio (OR) with 95% CI was calculated using a fixed-effect model.

We applied principles from GRADE to assess the evidence quality and address confidence in the effect estimates (Balshem 2011). When a meta-analysis is not viable due to varied interventions, a 'Summary of findings' table is not feasible. Therefore, we did not conduct a formal GRADE assessment with an evidence profile and 'Summary of findings' table (Guyatt 2011).

For the 2011 update, we added an assessment of evidence quality using the GRADE approach (Higgins 2011). This assessment was based on the quality of evidence from the individual studies. In 2014, we refined the criteria used, based on our subsequent experience with other reviews. Evidence quality could be high, moderate, low, or very low. We considered the evidence from RCTs to be high quality initially, then downgraded for each of the following: a) randomization sequence generation and allocation concealment: no information on either, or one was inadequate; b) lack of blinding; c) follow up was 12 months or less for BMD measures only; d) losses were greater than 20% for the primary analysis.

Sensitivity analysis

In 2014, we added a sensitivity analysis. This included trials that provided sufficient data and evidence of moderate or high quality.

RESULTS

Description of studies

Results of the search

The 2014 search produced 54 unduplicated citations from the main databases. In addition, we found seven unduplicated trials through

ClinicalTrials.gov and ICTRP. Three new trials were added, including one that had been 'ongoing' in the previous update (Cibula 2012; Gai 2012; Sordal 2012). In addition new ongoing trial was added (Bonny 2013). An earlier ongoing trial is still awaiting classification due to lack of a report (Teva 2013).

We identified 19 randomized controlled trials that met the criteria for inclusion. Bone density was measured in 17 trials; the other two assessed biochemical markers of bone turnover (Paoletti 2000; Rad 2011). Twelve studies assessed BMD as well as biochemical markers. None had fracture as an outcome. Of the 17 trials that examined BMD, 14 measured the lumbar spine using dual-energy X-ray absorptiometry (DEXA), although the measurement site varied somewhat. The other three studies with BMD used computed tomography for the lumbar spine (Endrikat 2004), DEXA for the arm (Bahamondes 2006), and single photon absorptiometry for the arm (Naessen 1995).

Included studies

Most of the studies were 12 to 24 months in duration and two were 36 months long (Endrikat 2004; Kaunitz 2009). One trial was limited to six months (Naessen 1995). A crossover trial had the participants switch COCs at 9 months for a total duration of 18 months (Cibula 2012). Three studies focused on adolescents (Cibula 2012; Cromer 2005; Gai 2012).

The types and formulations of hormonal contraceptives varied. Eleven trials compared different COCs or regimens of COCs:

- Two studied desogestrel-containing COCs (Berenson 2001; Gai 2012).
- Four examined levonorgestrel preparations as the investigational drug or the comparator (Endrikat 2004; Hartard 2006; Rad 2011; Sordal 2012).
- Three examined gestodene preparations (Paoletti 2000; Nappi 2003; Cibula 2012).
- Two examined drospirenone-containing COCs (Nappi 2005; Gargano 2008).

In addition, five trials examined an injectable versus another injectable, implant, or IUD (Naessen 1995; Von Kesseru 2000; Cromer 2005; Cundy 2003; Kaunitz 2009), two compared two implants each (Di 1999; Bahamondes 2006), and one studied the transdermal patch versus the vaginal ring (Massaro 2010).

Risk of bias in included studies

Allocation

Study design and reporting varied in quality across these trials.

Randomization information was as follows:

- Two trials had interactive voice-response systems, based on computer-generated random lists (Kaunitz 2009; Rad 2011).
- Most used a random numbers table or a computer for random-number sequence generation (Bahamondes 2006; Berenson 2001; Cibula 2012; Cromer 2005; Cundy 2003; Massaro 2010; Naessen 1995; Nappi 2003; Nappi 2005; Paoletti 2000; Von Kesseru 2000). Cromer 2005 mentioned block randomization techniques but did not specify the block size.
- Gai 2012 reported randomized by 'drawing lots' without further explanation.
- Five studies did not provide the method for sequence generation (Di 1999; Endrikat 2004; Gargano 2008; Hartard 2006; Sordal 2012).

Allocation concealment was unclear in many studies and not mentioned in others. As noted above, two had an interactive voice-response system (Kaunitz 2009; Rad 2011). Bahamondes 2006 reported having sealed envelopes prepared at the WHO, and Cromer 2005 communicated that they used serially-numbered opaque envelopes. Naessen 1995 used sealed envelopes, and Nappi 2005 reported the sequence was concealed until treatment was assigned. Two trials did not have any concealment and 11 trials had insufficient or no information.

Blinding

- Some blinding was used in six trials: double-blind (Cromer 2005; Cundy 2003; Endrikat 2004); investigators and providers (Kaunitz 2009); laboratory personnel (Massaro 2010); and participants (Berenson 2001).
- Six trials were open-label (Hartard 2006; Nappi 2005; Paoletti 2000; Rad 2011; Sordal 2012; Von Kesseru 2000).
- Information on blinding was not available from seven studies (Bahamondes 2006; Cibula 2012; Di 1999; Gai 2012; Gargano 2008; Naessen 1995; Nappi 2003).

Incomplete outcome data

Losses were high in several trials, but largely due to method discontinuation or missing data. Losses greater than 20% threaten trial validity (Strauss 2005).

- In Von Kesseru 2000, loss of participants or missing data for BMD at 12 months was 48% and 79% in the two intervention groups. At 24 months, the figures were 70% and 84%.
- Berenson 2001 losses were attributed to discontinuation or failure to obtain a bone scan within the required window: at 12 months, 62% and 68% for the two intervention groups; at 24 months, 71% and 54%.
- In Endrikat 2004, loss was 52% at 36 months with 61% loss for bone data.
- Cundy 2003 had a 29% loss due to early discontinuation.
- In Cromer 2005, 24% withdrew by 12 months and 43% withdrew by 24 months. This does not include those without assessments due to early study closure.
- Three trials had high overall losses: Kaunitz 2009 (39%); Rad 2011 (29%); Sordal 2012 (41%); losses to follow up were under 20%.

Effects of interventions

Progestin-only methods

Six trials examined methods containing only the hormone progestin, including two trials of implants and four that examined the studied DMPA 150 mg.

Implants

- Di 1999 examined the six-capsule Norplant versus a similar domestic implant (manufactured in China). BMD at Ward's triangle was higher among Norplant users than domestic implant users at 12 months (mean difference (MD) 0.07; 95% CI 0.00 to 0.14, Analysis 1.4). Both types of implants had six

capsules with the same amount of levonorgestrel. The groups did not differ significantly for BMD at the other locations, nor for serum and urinary measures.

- In Bahamondes 2006, the implants studied were a single-rod etonogestrel-releasing implant and a two silicone rod levonorgestrel-releasing implant. By 18 months, the etonogestrel-implant group had a greater percent decrease in BMD at the midshaft ulna than the two-rod levonorgestrel group (MD -0.39; 95% CI -0.56 to -0.22, Analysis 2.2) and at the distal radius (MD -1.00; 95% CI -1.09 to -0.91, Analysis 2.4). A secondary paper reported on BMD at 36 months, but the losses to follow up by that time were large and the groups were not significantly different for BMD at the distal radius.

Injectable DMPA 150 mg

- Naessen 1995 randomized women to either DMPA 150 mg every 12 weeks or the levonorgestrel implant (Norplant). The DMPA group had a lower mean for alkaline phosphatase, a marker of bone formation, than the implant group at six months (MD -0.65; 95% CI -1.21 to -0.09, Analysis 3.1). The groups did not differ significantly for serum osteocalcin and calcium and for urinary hydroxyproline/creatinine. BMD data were shown in a figure rather than a table. By six months, BMD at the forearm reportedly increased in the levonorgestrel implant group (reported P = 0.006) and decreased insignificantly in the DMPA group. The group difference was reportedly significant at the proximal (reported P = 0.025) but not the distal forearm.
- Two trials examined estrogen supplement versus a placebo for women on DMPA. All participants had an injection of DMPA 150 mg every 12 weeks.
  - In Cromer 2005, one DMPA group received monthly injections of estradiol cypionate (E_2C) 5 mg whereas the other received the placebo supplement of 5 mL normal saline solution. Bone mineral apparent density (BMAD) was used to correct for variation in bone (see Characteristics of included studies). At 12 months, the groups with the estrogen supplement had increases while the placebo-supplement group had decreases for spine BMD (MD 2.90; 95% CI 1.80 to 4.00, Analysis 4.1), spine BMAD (MD 2.70; 95% CI 1.60 to 3.80, Analysis 4.2), and femoral neck BMD (MD 3.20; 95% CI 1.36 to 5.04, Analysis 4.3). The groups were not significantly different for femoral neck BMAD (Analysis 4.4). At 24 months, the same trend was seen: spine BMD (MD 4.60; 95% CI 2.87 to 6.33, Analysis 4.5), spine BMAD (MD 4.90; 95% CI 3.11 to 6.69, Analysis 4.6), femoral neck BMD (MD 9.80; 95% CI 4.96 to 14.64, Analysis 4.7), and femoral neck BMAD (MD 7.10; 95% CI 0.50 to 13.70, Analysis 4.8). The trial was stopped early due to the differences reaching the predetermined significance level (P < 0.001).
  - Cundy 2003 randomized DMPA users to daily intake of conjugated estrogens 62.5 µg or to a placebo supplement. BMD was measured at the lumbar spine, femoral neck, Ward's triangle, trochanter, and total body. For lumbar spine BMD, the group with the estrogen supplement had a small increase and the placebo-supplement group had a small decrease by 12 months (MD 0.02; 95% CI 0.00 to 0.04, Analysis 5.1) and by 24 months (MD 0.04; 95% CI 0.02 to 0.06, Analysis 5.2). More than a fourth of the participants discontinued early. No significant changes were reportedly apparent in plasma calcium, phosphate, or alkaline phosphatase activity or in urinary N-telopeptides/creatinine.
- In Kaunitz 2009, intramuscular DMPA 150 mg/mL (DMPA-IM) was compared with subcutaneous DMPA 104 mg/0.65 mL (DMPA-SC). The groups did not differ significantly in the proportions with a 5% or greater decrease in total hip BMD at one, two, or three years. For lumbar spine BMD, more of the DMPA-SC group had a 5% or greater decrease by year 3 (OR 2.11; 95% CI 1.00 to 4.45, Analysis 6.6). Losses due to discontinuation were high.

Combination contraceptives

These 13 trials included 11 that compared combined oral contraceptives, as well as one of a combination injectable versus a non-hormonal IUD and one of the transdermal patch versus the vaginal ring.

Oral contraceptives

Two compared desogestrel-containing COCs versus other COCs:

- Berenson 2001 randomized women to norethindrone 1 mg plus ethinyl estradiol (EE) 35 µg or to desogestrel 150 µg plus EE 30 µg. The norethindrone group had a significantly greater increase in BMD at the lumbar spine at 12 months than the desogestrel group (MD 1.83; 95% CI 0.42 to 3.24, Analysis 7.1). By 24 months, both groups had decreases from baseline but they were not significantly different. However, only about one-third of the original participants remained at 12 months.
- Gai 2012 also used desogestrel 150 µg plus EE 30 µg, but the comparison was cyproterone acetate (CPA) 2 mg plus EE 35 µg. The group with the desogestrel-containing COC did not differ significantly from the CPA group for the BMD measures of lumbar spine or femoral neck at 12 or 24 months (Analysis 8.1 to Analysis 8.4).

Four trials used preparations containing levonorgestrel, either as the investigational drug or the comparator:

- Endrikat 2004 compared levonorgestrel 100 µg plus 20 EE µg versus levonorgestrel 150 µg plus EE 30 µg. The two groups did not differ significantly in their slight decreases in BMD at 36 months (Analysis 9.1 to Analysis 9.4). Serum alkaline phosphatase increased and N-telopeptides decreased, but change did not differ significantly between the groups. More than half of the participants were lost to follow up.
- Hartard 2006 examined levonorgestrel 100 µg plus 20 EE µg versus desogestrel 150 µg plus EE 20 µg. By 12 months, the desogestrel group lost more areal BMD at the lumbar spine than the levonorgestrel group, but the difference was small (MD 1.41; 95% CI -0.11 to 2.93, Analysis 10.1). The desogestrel group had a greater decrease in serum alkaline phosphatase (MD 15.31; 95% CI 3.91 to 26.71, Analysis 10.3). The groups did not differ significantly in change in areal BMD at the femoral neck or in serum osteocalcin or C-telopeptides (Analysis 10.2; Analysis 10.4; Analysis 10.5).
- Rad 2011 compared a continuous regimen of levonorgestrel 90 µg plus EE 20 µg versus a cyclic regimen of levonorgestrel 100 µg plus EE 20 µg. The report provided standard errors and did not contain cell sizes, so we could not analyze any data. Reportedly, changes in osteocalcin and C-telopeptides were not significantly different between the groups by cycle 13.

- For Sordal 2012, the COC of interest was nomegestrol 2.5 mg plus [17ß] estradiol 1.5 mg (NOMAC-E2), and the comparison was levonorgestrel 150 µg plus EE 30 µg. By cycle 26, the groups did not differ significantly for change in z-score of the lumbar spine (Analysis 11.1) or femoral neck (Analysis 11.2).

Gestodene-containing COCs were the focus of three trials:

- Paoletti 2000 randomized women to gestodene 75 µg plus EE 20 µg or gestodene 75 µg plus EE 30 µg. At 12 months, urinary deoxypyridinoline was lower in the EE 30 µg group than in the EE 20 µg group (MD 1.20; 95% CI 0.37 to 2.03, Analysis 12.2). The study groups were not significantly different for serum osteocalcin and urinary pyridinoline.
- Nappi 2003 studied gestodene 75 µg plus EE 20 µg versus gestodene 60 µg plus EE 15 µg. The results were presented in figures without absolute values. The investigators reported no significant difference at 12 months between or within the groups in BMD at the lumbar spine or in serum osteocalcin. The study groups reportedly had significant declines in urinary pyridinoline and deoxypyridinoline by 6 and 12 months (reported $P < 0.05$), but the groups did not differ significantly.
- The crossover study of Cibula 2012 compared gestodene 75 µg plus EE 30 µg versus gestodene 60 µg plus EE 15 µg. The participants were switched to the other formulation at nine months; study duration was 18 months. Measures included BMD of the lumbar spine, femur, and distal radius, as well as serum type I procollagen (PINP) and type I collagen cross-linked C-telopeptide (ßCTX1). The report included results of the full analysis of variance model (ANOVA) for lumbar BMD, PINP, and ßCTX1 (Table 3). Reportedly, dose was significantly associated with change in lumbar BMD (reported F-ratio = 4.6; reported P value = 0.037). The COC containing EE 30 µg showed an increase while the COC containing EE 15 µg showed a decrease. Dose was also reportedly associated with a difference in PINP (reported F-ratio = 8.3; reported P value = 0.005), but the text and figure were inconsistent regarding the direction of change. For ßCTX1, no significant difference was reported.

Drospirenone-containing COCs were examined in two trials:

- Nappi 2005 examined drospirenone 3 mg plus EE 30 µg versus gestodene 75 µg plus EE 30 µg. Bone mineral density at the lumbar spine did not differ significantly between the two groups at 12 months (Analysis 13.1). Data for biochemical markers were presented in figures without absolute numbers. Reportedly, the groups did not differ significantly for urinary pyridinoline or deoxypyridinoline but both groups decreased significantly. Serum calcium reportedly increased significantly in the drospirenone-COC group and was significantly different from that gestodene-COC group. Reportedly, other changes in serum and urinary calcium were not significant. The investigators also reported that serum osteocalcin did not change significantly; within-group changes were not mentioned.
- Gargano 2008 compared drospirenone 3 mg plus EE 30 µg versus drospirenone 3 mg plus EE 20 µg. BMD at the lumbar spine did not differ significantly between the two groups at 12 months (Analysis 14.1). Biochemical measures were shown in figures without absolute numbers. The investigators reported the study groups were not significantly different at 12 months for urinary pyridinoline and deoxypyridinoline but that both groups decreased significantly. They also reported that no significant difference between groups for serum or urinary calcium or for serum osteocalcin. Reportedly, both groups had significant increases in serum calcium but changes within group were not significant for the other measures.

Injectable versus non-hormonal IUD

Von Kesseru 2000 compared monthly injections of norethisterone enanthate 50 mg plus estradiol valerate (E_2V) 5 mg versus the Nova-T IUD. Bone density did not differ significantly between the injectable group and the IUD group at 24 months (Analysis 16.1, Analysis 16.2). The trial focused on serum lipid patterns; bone density was of secondary interest. Only half the women were assigned to have bone density measures, and many did not have outcome data. Changes in BMD were modest but positive. However, the analyzed groups were so small due to high losses that the results may not be meaningful.

Patch versus ring

Massaro 2010 compared the contraceptive patch delivering norelgestromin 150 µg plus EE 20 µg daily versus the vaginal ring releasing etonogestrel 120 µg plus EE 15 µg daily. At 12 months, the study groups did not differ significantly in spinal BMD, urinary pyridinoline, urinary deoxypyridinoline, and serum osteocalcin (Analysis 15.1 to Analysis 15.4). Spinal BMD did not change much from baseline, while the biochemical markers generally had changes that were positive for bone health.

DISCUSSION

Summary of main results

We summarized the results by contraceptive method and composition (Table 4). Two studies of DMPA plus a supplement were placebo-controlled, and one study compared a combination injectable to a non-hormonal IUD. Since the estrogen preparations and routes of administration differed for the DMPA trials, we did not conduct a meta-analysis. Nonetheless, the two trials showed BMD increases for the women who received DMPA plus estrogen supplement and decreases for those who had DMPA plus placebo supplement. In the combination injectable study, BMD changes were modest but the losses were too high for results to be informative.

Most trials compared two different hormonal contraceptives. Combination oral contraceptives did not appear to negatively affect bone density, and some formulations had more positive effects than others. However, none were placebo-controlled. Where trials showed differences between groups in biochemical markers of bone formation, the results were generally consistent with those for bone mineral density. For the progestin-only implants, two trials studied different implants, used different sites for measuring BMD, and had varying durations. One study showed a greater decrease in BMD for the etonogestrel-implant group than the two-rod levonorgestrel group.

Sensitivity analysis

We assessed the quality of the evidence, as discussed below (Table 1). Our sensitivity analysis had 11 trials that provided sufficient data for the outcome and evidence of moderate or high quality (Table 2). These included the four DMPA studies, the two implant trials, the combination injectable and patch versus study, but only 3 of the 11 COC trials. The results were similar to those for the review

overall. Of the four DMPA-IM trials, two showed a positive effect of an estrogen supplement on BMD, one had a negative effect of DMPA-SC on lumbar spine BMD, and the fourth indicated a negative effect of DMPA-IM on a bone formation marker. The two implant studies each had one significant difference in BMD out of several measures. Of the three COC trials, two examined BMD, of which one showed a decrease for the group with gestodene plus EE 15 µg. Of the two that used biochemical measures, one indicated less bone resorption in the group with gestodene plus EE 30 µg versus EE 20 µg. No significant differences were noted in the trials of the combination injectable or the patch versus ring.

Overall completeness and applicability of evidence

None of the studies included fracture as an outcome. Longer follow up would be needed for meaningful assessment of fracture. Since fragility fractures are rare in young people, fracture is not usually an outcome in studies of premenopausal bone health (Gourlay 2004). Researchers and clinicians may have to rely on bone mineral density and biochemical measures of bone health. BMD correlates with fracture but is not a valid surrogate endpoint for fracture (Grimes 2010). BMD is considered useful in screening for osteoporosis in postmenopausal women. However, its validity in assessing risk is still unclear for premenopausal women, including those using steroidal contraceptives (Nappi 2012). International organizations have recommended using bone turnover markers rather than BMD for monitoring treatment of osteoporosis (Vasikaran 2011a). In this review, markers of bone formation included serum alkaline phosphatase, osteocalcin, and type I procollagen; bone resorption indicators included serum calcium and C-telopeptide as well as urinary pyridinoline and N-telopeptides. Recommended reference markers are serum procollagen type I N propeptide, s-PINP (bone formation); and serum C-terminal cross-linking telopeptide of type I collagen, s-CTX (bone resorption) (Vasikaran 2011a; Vasikaran 2011b). Decreases in these markers correlate better than others with reduction in fracture risk. However, the relationship of hormonal contraceptive use and bone health is less well understood (Herrmann 2010).

Methodological differences limited the analysis and interpretation of the data. Due to the differing interventions studied, no trials were combined for meta-analysis. Studies compared COCs with different formulations, two types of implants, injectables with other methods, and the skin patch with the vaginal ring. Such differences in treatments limit the conclusions about any one contraceptive method.

Of 19 studies, only 3 were limited to adolescents (Cromer 2005; Cibula 2012; Gai 2012); a fourth focused on young women (Hartard 2006). Three of those four trials showed some differences between study groups in BMD or bone turnover markers, compared to 7 of the 15 studies with older women. Adolescents are rapidly acquiring bone mass (Cibula 2012; Nappi 2012). Whether COCs affect the development of peak bone mass is unclear, though COCs with less than 30 µg EE may be a concern (Nappi 2012). DMPA may affect BMD in adolescents, but some studies have indicated a return to baseline after discontinuation (Kaunitz 2011; Nappi 2012). More studies focused on adolescents and younger women would be useful. However, placebo-controlled trials in contraception are limited for ethical reasons, especially among a population at high risk for unplanned pregnancy.

Quality of the evidence

As noted earlier, we refined our criteria to identify the specific risk of bias issues in 2014 (Assessment of risk of bias in included studies). For this review, the evidence quality was considered moderate overall (Table 1). The DMPA studies provided moderate quality evidence. The quality of the COC evidence varied widely, but was considered low overall. The quality was moderate to high for the studies of implants, combination injectable, and patch versus ring.

Limitations of these studies include incomplete or no description of sequence generation and allocation concealment, lack of blinding, and high losses. Some reports did not have sufficient data for assessment; outcomes were presented in tables without absolute numbers. For losses, we could not always distinguish between losses to follow up or discontinuation. Therefore, we included all losses in our assessment. About half of the trials had high losses, so the results may not represent randomized comparisons. As noted earlier, losses greater than 20% can bias the results and threaten trial validity (Strauss 2005). At least three trials lost more than half the participants and some had differential losses between the comparison groups.

Agreements and disagreements with other studies or reviews

A review of observational studies did not indicate an overall association between OC use and fracture risk, except for some increased risk among specific user subgroups (Lopez 2012). As noted earlier, COCs may have little effect on BMD among healthy adult women (Herrmann 2010; Warholm 2012). BMD in adolescent and young women may be affected by the use of COCs with lower estrogen doses, i.e., 20 µg (Nappi 2012). COC use may have a negative effect on bone turnover markers, although the clinical significance of such change is unclear (Herrmann 2010).

Of progestin-only methods, DMPA has been associated with decreased bone mineral density (Nappi 2012). However, no published RCT has linked DMPA use with fracture later in life. A review of observational studies had two case-control studies in the sensitivity analysis that examined DMPA (Lopez 2012). One of the studies reported increased fracture risk for DMPA ever-use, more than four years of use, and women over 50 years of age. The other noted increased risk for any past DMPA use and for current use of 3 or more prescriptions. A loss of BMD during adolescence may be recovered after discontinuing DMPA (Kaunitz 2011; Nappi 2012). The changes may be transient like those occurring during pregnancy or lactation (ACOG 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Whether steroidal contraceptives influence fracture risk cannot be determined from existing information. Combination contraceptives do not appear to negatively affect bone mineral density or bone turnover markers. Of progestin-only methods, DMPA may alter bone mineral density. Whether DMPA affects fracture risk cannot be determined, as no randomized trial assessed fracture. Health care providers and women should consider the costs and benefits of these effective contraceptives. The advantages of DMPA outweigh concerns about fracture risk for adolescents and for women over 45 years of age (WHO 2009). Injectable contraceptives may be appropriate for women who

want long-term birth control without a daily regimen. Other candidates for progestin-only contraceptives are women with contraindications to estrogen use.

Implications for research

Additional trials of estrogen supplementation with progestin-only contraceptives would provide more evidence regarding any effect on bone health. Many trials had limitations for interpretation, including small numbers of participants and large losses. Stronger evidence is needed to make recommendations for clinical practice. Trials of longer duration could provide information on whether there was any reversal of earlier decreases in BMD. Studies could focus on adolescents, who have not yet reached peak bone mass, and on perimenopausal women, who may be losing bone mass. Results of such trials could help determine if these two groups are at greater risk of adverse outcomes due to the effects of progestin.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bahamondes 2006

Methods	Randomized controlled trial; enrollment from Aug 2003 to Jul 2004.

Bahamondes 2006 *(Continued)*

	Sample size calculation based on assuming a BMD change of 0.014 g/cm^2 by 18 months; 48 women per group would provide 80% power to detect difference of 0.008 (presumably between groups).
Participants	111 women, 19 to 43 years, requesting implant for contraception. Women were a subset of a larger study by UNDP/UNFPA/World Bank/WHO. Inclusion criteria: not pregnant or lactating within 12 months of enrollment. Exclusion criteria: women with chronic diseases, such as diabetes mellitus, chronic renal failure, hyper/hypothyroidism, hyper/hypoparathyroidism, hepatitis, cancer or pituitary disease. Also excluded were women who used calcium or Vitamin D supplements, anticonvulsants, any corticosteroids, thiazide diuretics or drugs for thyroid disease.
Interventions	1) Single-rod etonogestrel-releasing implant (Implanon, NV Organon, Oss, Netherlands) (N=56) versus 2) Two silicone rod levonorgestrel-releasing implant (Jadelle; Schering Oy, Turku, Finland) (N=55). Insertions performed in first 5 days of cycle; no wash-out period for those with previous contraception. [9 women had amenorrhea at insertion due to DMPA use.] Duration: 18 months
Outcomes	Bone mineral density (BMD) at midshaft of ulna (mainly cortical bone) and at distal radius (mainly trabecular bone). Measures done in non-dominant arm with DEXA. Measures taken at baseline and 18 months. Later report (Monteiro-Dantas, 2007) provided 36-month data for BMD at distal radius (also ultra-distal radius, not available in earlier report and not used in this review).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization system
Allocation concealment (selection bias)	Low risk	Allocation concealment with sealed envelopes prepared at WHO
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses: 18 months, all participants included in analysis (primary paper); 36 months (secondary paper), loss was 32% (36% Implanon and 29% Jadelle).

Berenson 2001

Methods	Randomized controlled trial in USA; recruitment from May 1996 to Jan 1999.
Participants	179 women, 18 to 33 years, who had undergone baseline bone scan as part of larger contraceptive study. Inclusion criteria: due to funding (US Department of Defense), women had to meet criteria for entry into armed forces (high school graduate or equivalency diploma, no felony arrests, within 36% ideal body weight for height, free of medical conditions or physical disabilities that would affect completion of military training).

Berenson 2001 *(Continued)*

	Exclusion criteria: currently pregnant or breastfeeding, had injection for contraception in past 6 months, took OCs in past month, or had medical contraindication to hormonal contraception.
Interventions	1) Ethinyl estradiol 35 µg plus norethindrone 1 mg OC (Ortho Novum 1/35; Ortho Pharmaceutical Corporation, New Brunswick, NJ) (N=87) versus 2) Ethinyl estradiol 30 µg plus desogestrel 150 µg OC (Mircette; Organon Corporation, Oss, Netherlands) (N=92). Data were reported for 28 and 35 women at 12 months.
Outcomes	Bone mineral density of lumbar spine (L1 to L4) with DEXA at baseline and at 12 months. Baseline scans performed within 2 months of initiation; follow-up scans were done 10 to 14 months after baseline. Berenson 2004 reported on scans at 24 months for those who obtained a second scan.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table used
Allocation concealment (selection bias)	High risk	No allocation concealment, according to communication with investigator.
Blinding (performance bias and detection bias) All outcomes	Low risk	Providers not blinded to treatment; package labeling was removed for participants. Pills were referred to as "red" or "green."
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses due to discontinuation of contraceptive method or failure to have bone scan (at all or within required window): at 12 months, 68% for norethindrone-containing pill and 62% for desogestrel-containing pill; at 24 months, 71% and 54%, respectively.

Cibula 2012

Methods	Randomized, crossover trial; investigators from Czech Republic. No a priori sample size calculation. Reportedly had post hoc power analysis; no detail provided.
Participants	56 adolescent females who requested hormonal contraception at adolescent gynecology unit. Inclusion criteria: age 15 to 19.5 years, BMI 20 to 27 kg/m^2, regular menstrual cycle. Exclusion criteria: recent or past COC use; systemic or chronic diseases including endocrine disorders; using medication that could influence bone metabolism or reliability of hormonal contraception (e.g. corticosteroids, antiepileptics, thyroid hormones); drug use or smoking > ten cigarettes per day; daily dietary calcium intake < population average (< 600 mg/day); endurance physical activity; immobilization or invalidity; COC contraindication.
Interventions	1) Gestodene 75 µg plus EE 30 µg versus 2) Gestodene 60 µg plus EE 15 µg Groups switched COCs after 9 months of use; total study duration was 18 months.

Cibula 2012 *(Continued)*

	No 'washout' period between study periods, reportedly for ethical reasons, i.e., high risk of pregnancy among adolescents.
Outcomes	BMD at lumbar spine L1 to L4, total proximal femur, femoral neck and distal radius, total body mineral content. Reported median and quartiles for percent changes from baseline. Serum propeptide of type I procollagen (PINP, bone formation marker). Serum type I collagen cross-linked C-telopeptide (ßCTX1, bone resorption marker). Percent changes in biochemical outcomes shown in figures without absolute values.
Notes	Control group of nonusers did not want hormonal contraception (not included here). Unable to obtain further data from investigator regarding outcomes, e.g., means and SD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers (STATA software).
Allocation concealment (selection bias)	Unclear risk	no information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	no information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss by 9 months: group 1, EE 15 µg 3/28 = 10.7%; group 2, EE 30 µg 3/28 = 10.7%; Loss by 18 months (after crossover): group 1, EE 30 µg 6/28 = 21.4%; group 2, 5/28 = 17.9%; total loss 19.6%.

Cromer 2005

Methods	Randomized controlled trial in the USA; 4 health clinics in large metropolitan setting Enrollment from May 2000 to Dec 2002. No sample size calculation provided
Participants	123 adolescent females. Inclusion criteria: adolescent girls, age 12 to 18 years, who were seeking contraception and selected DMPA. Exclusion criteria: use of DMPA, pregnancy or abortion in past 6 months; use of OCs in past 3 months, chronic medical condition or treatment that may affect bone, or need for confidentiality in contraception.
Interventions	All participants: DMPA as 150 mg deep intramuscular injection every 12 weeks. 1) Monthly intramuscular injections of 5 mg estradiol cypionate (supplement) (N=65) versus 2) 5 mL normal saline solution (placebo) (N=58). Study duration: 24 months
Outcomes	Bone mineral density obtained at L1 to L4 lumbar vertebrae, total hip (left), femoral neck, trochanter, and Ward's triangle; DEXA was used.

Cromer 2005 *(Continued)*

	Bone mineral apparent density (BMAD) was used to correct for variation in bone: BMAD = BMC(L1 to L4) / $Ap^{3/2}$, where BMC = scanned bone mineral content and Ap = projected area; BMAD = BMC(femoral neck) / Ap^2(femoral neck). Outcome means were adjusted for baseline body weight and bone mineral density.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by recruitment site. 'Blocked randomization techniques.'
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded: study subjects, technicians conducting the dual energy x-ray absorptiometry scans, and clinicians providing health care to the participants Nurse providing injections was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial was stopped early due to interim analysis showing the differences between the groups reached the pre-determined significance level of < 0.001. Estrogen supplementation was offered to participants who had the placebo; exercise and diet counseling was offered to all active participants. Many participants had not had 12 or 24 months of observation (N=24 and N=33, respectively). In addition, 30 young women withdrew by 12 months (30/123 = 24%) and 53 withdrew by 24 months (53/123 = 43%).

Cundy 2003

Methods	Randomized controlled trial in Auckland, New Zealand. Analysis by intention to treat.
Participants	38 women recruited from family planning clinics. Inclusion criteria: age <= 45 years, long-term users (>= 2 years) of DMPA, areal BMD (from lumbar spine) <= 1.20 g/cm2 (young adult average). Exclusion criteria: known metabolic bone disease, taking drugs (other than DMPA) that can affect bone density, FSH > 20 U/liter.
Interventions	All participants: DMPA 150 mg injection every 12 weeks. 1) Conjugated estrogens 62.5 µg (Premarin; Wyeth-Ayerst, Collegeville, PA) (N=19) versus 2) Placebo (N=19), taken orally each day for 2 years. Duration: 24 months
Outcomes	Areal BMD by DEXA at lumbar spine (L2 to L4), femur, and total body; lumbar spine BMD was the primary outcome. Results were reported for plasma calcium, phosphate, total alkaline phosphatase activity; fasting urine N-telopeptide/creatinine ratio.

Cundy 2003 *(Continued)*

Notes	Author provided data for all BMD measures (article had graphs) as well alkaline phosphatase (AP) and N-telopeptide NT. However, AP and NT had missing data at baseline, and the distributions appeared to be skewed, so those data were not analyzed in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to the investigator, randomization was balanced by blocks of 10; within a block, subject was "allocated a treatment number." Random numbers above the median were assigned to treatment and those below were assigned to placebo.
Allocation concealment (selection bias)	Low risk	According to communication with the investigator, allocation concealment was accomplished with serially-numbered opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	High risk	27 women completed 18 months or more (29% loss to early discontinuation from study)

Di 1999

Methods	Randomized controlled trial in Beijing.
Participants	61 women, aged 25 to 40 years, who sought contraception counseling at Ob-Gyn Hospital. Inclusion criteria: regularly menstruating, no OC use in past 3 months or Norplant removed >=6 months prior, no medications or diseases known to interfere with bone metabolism.
Interventions	1) Norplant implant (Leiras Pharmaceuticals, Turku, Finland) (N=30) versus 2) Domestic implant (Capsulae Levonorgestreli Silasticus; Yalujiang Medical Factory, Dandong, Laioning Province, China) (N=31). Both types had 6 capsules, each with 36 mg levonorgestrel for a maximum 216 mg levonorgestrel. Study duration 1 year
Outcomes	BMD of lumbar spine (L2 to L4) and proximal femur via DEXA. Serum osteocalcin (BGP) and alkaline phosphatase (ALP); urine hydroxyproline/creatinine and urine calcium/creatinine.
Notes	Attempts to reach the investigator were unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomly divided into two groups
Allocation concealment (selection bias)	Unclear risk	No information

Di 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	One implant removed at subject's request and data excluded from analysis.

Endrikat 2004

Methods	Randomized controlled trial in Germany Analysis was per protocol.
Participants	100 healthy women at one center. Inclusion criteria: current users of COCs for > 2 years, but no EE >= 50 µg for more than 6 months; started COCs after 16th birthday. Exclusion criteria: contraindications for COC use; smoking >15 cigarettes for women < 30 years and any smoking for women > 30 years; use of DMPA in previous 6 months, use of other sex hormones during treatment, coexisting diseases (unspecified), diagnostically unclassified genital bleeding, and history of migraine with menstruation.
Interventions	1) 20 µg ethinyl estradiol (EE) plus 100 µg levonorgestrel OC (20/100; Schering AG, Berlin, Germany) versus 2) 30 µg ethinyl estradiol with 150 µg levonorgestrel OC (30/150; Schering AG). First tablet taken on first day of withdrawal bleeding with no wash-out period. 36 consecutive 28-day cycles. Study duration was 3 years
Outcomes	Trabecular BMD of lumbar spine (L1 to L3) using computed tomography; alkaline phosphatase and N-telopeptides.
Notes	Attempts to reach the investigator were unsuccessful

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	High risk	88 took at least one dose; authors' analysis only included the 48 who provided data at baseline and cycle 36 (52% loss). Loss to follow up was 15% overall (15/100). Bone density data provided for the 39 with data at all time points (61% loss).

Gai 2012

Methods	Randomized trial; unspecified location (protocols approved in Shandong, China). No sample size calculation provided.
Participants	300 women from 16 to 18 years old, attending family planning clinics and requesting birth control. Inclusion criteria: regular menses, non-hormonal contraception, no breastfeeding or delivery for at least 6 months, no pregnancy; did not take calcium, vitamin D, or bone-affecting medication. Exclusion criteria: chronic disease, such as diabetes mellitus, renal dysfunction, thyroid and parathyroid diseases, hepatitis or pituitary diseases.
Interventions	1) Desogestrel (DSG) 150 µg plus EE 30 µg versus 2) Cyproterone acetate (CPA) 2 mg plus EE 35 µg Duration: 2 years
Outcomes	BMD measured at lumbar spine (L 2 to L4) and femoral neck by DEXA.
Notes	A third group was not randomized; women did not want to use hormonal method.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	By 'drawing lots'
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss by 12 months: DSG+EE 12/150 = 8%; CPA+EE 11/150 = 7.3%. Loss by 24 months: DSG+EE 23/150 = 15.3%; CPA+EE 16/150 = 10.7%.

Gargano 2008

Methods	Randomized trial in Italy No sample size calculation provided.
Participants	44 women, 21 to 34 years old, presenting at clinic. Inclusion criteria: age of menarche 12 to 14 years, ovulation during pretreatment cycle, BMI > unclear (report had error in lower cutoff of '2') < 25, normal menstrual cycles, normal diet without high or low caloric intake. Exclusion criteria: confirmed or suspected pregnancy, pregnancy or breastfeeding in past year, liver disease, vascular or metabolic disorder, disorder of bone metabolism, treatment with drugs that affect bone metabolism or drugs that interfere with contraceptive steroids, other contraindication for COCs.
Interventions	1) Drospirenone 3 mg plus EE 30 µg versus 2) Drospirenone 3 mg plus EE 20 µg

Gargano 2008 *(Continued)*

	Duration of 12 months
Outcomes	BMD of lumbar spine (L1 to L4) by DEXA. Bone turnover markers: serum and urinary calcium, urinary pyridinoline and deoxypyridinoline (resorption); serum osteocalcin (formation). Results were presented in figures, without absolute values, for urinary pyridinoline and deoxypyridinoline and for serum osteocalcin.
Notes	'Controls' were not randomized, and therefore were excluded from analysis in this review; they did not request contraception. Unable to obtain from investigator further information on methodology or additional data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses: 7% (3/44) included 1 excluded for protocol violation (EE 30 µg group) and 2 early discontinuations (EE 20 µg group).

Hartard 2006

Methods	Randomized trial in Munich, Germany No mention of sample size calculation or power.
Participants	52 women, 18 to 24 years old, recruited via advertisements and mass mailings. Inclusion criteria: discontinued OCs for at least 2 months; spontaneous menstrual cycle during run-in period. Exclusion criteria: BMI > 30, history of smoking (>20 cigarettes/day), alcohol consumption (>20 g/day), exercise > 1 hour/week in past, age of menarche > 15 years, long-term use of OC (> 50% of time since menarche), previous menstrual disorders, past or current pregnancy, hypertension (> 140/90 mmHg), abnormal values for clinical chemistry, current or past medication with drugs that influence bone metabolism, use of contraceptive implants in past 6 months, diseases that affect bone (except well-controlled Type I diabetes mellitus or well-controlled hypothyroidism)
Interventions	1) Levonorgestrel 100 µg plus EE 20 µg (N=24) versus 2) Desogestrel 150 µg plus EE 20 µg (N=28); Duration of 13 cycles
Outcomes	BMD (spine L2 to L4 and femoral neck) by DXA. Serum bone-specific alkaline phosphatase; intact osteocalcin; serum C-terminal cross-linked telopeptides.

Hartard 2006 *(Continued)*

Notes	'Controls' were not randomized, and therefore were excluded from the analysis in this review; they did not choose hormonal contraception.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses due to discontinuation (e.g., adverse events, personal reasons): 19%; desogestrel group, 21%; levonorgestrel group, 17%.

Kaunitz 2009

Methods	Randomized controlled trial at 36 sites in USA, 9 sites in Canada, and 3 sites in Brazil; conducted from 2001 to 2004. Sample size of 250 for each group was based on 80% power to detect 2% difference in bone mineral density at 2 years.
Participants	535 women aged 18 to 35 years, sexually active, desiring long-term contraception. Inclusion criteria: regular menstruation in past 3 months, negative urine pregnancy test, and willingness to rely upon DMPA-SC or DMPA-IM for contraception for at least 2 years. Exclusion criteria: use of oral contraceptives, implant, or hormonal IUD in past 2 months or DMPA-IM in past 10 months (contraceptive patches and rings were not in use at the time of study enrollment); lumbar spine or femur BMD T-score of less than −1.0, history of pathologic or compression fracture; abnormal cervical cytology; undiagnosed abnormal genital bleeding; known or suspected pregnancy; history of breast cancer, thrombotic event, hepatic or renal disease, alcoholism or other drug abuse (in past 5 years); uncontrolled hypertension, active hepatic or renal disease, type 1 diabetes, or poorly controlled type 2 diabetes; and taking anticancer agent aminoglutethimide. Calcium, multivitamins, and other mineral supplements were not required nor prohibited if part of the participants' normal daily regimen.
Interventions	1) DMPA 104 mg/0.65 mL by subcutaneous injection every 3 months (DMPA-SC) versus 2) DMPA 150 mg/mL by intramuscular injection every 3 months (DMPA-IM) Duration: 2 years; secondary objectives included assessing efficacy, safety, and tolerability over 3 years
Outcomes	Primary: percent change (baseline to 2 years) in BMD at total hip and lumbar spine; dual X-ray absorptiometry used. Efficacy endpoint was pregnancy (urine test). Adverse events recorded throughout study.

Kaunitz 2009 *(Continued)*

Notes	Study was sponsored by Pfizer. Three investigators were not compensated, investigators reportedly retained full editorial control over content of paper; other 2 were Pfizer employees. Report did not specify where the analysis was conducted or by whom.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice-response system based on computer-generated random list
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators and evaluators at each site were blinded. Independent person received the study syringes, maintained the randomization code, and administered the study drug.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participant flow chart provided. Overall losses by 1 year: 39% (38% DMPA-SC, 40% DMPA-IM). Loss to follow up by 2 years (1 year not available): 19% overall; 16% DMPA-SC, 22% DMPA-IM Efficacy analysis included all participants who received at least one dose of study drug and made at least one visit after receiving study drug.

Massaro 2010

Methods	Randomized controlled trial at university-based family planning clinic in Italy during 2008. No mention of sample size calculation.
Participants	40 healthy women, 23 to 34 years old, requesting contraception. Inclusion criteria: age of menarche 12 to 14 years, demonstrable ovulation during pretreatment cycle, body mass index (BMI) > 20 and < 22 kg/m^2, normal menstrual cycles and normal diet. Exclusion criteria: confirmed or suspected pregnancy, pregnancy or breastfeeding in past year, liver disease, vascular or metabolic disorder, disorder of bone metabolism (Paget disease, hyperparathyroidism, renal osteodystrophy) and treatment with drugs that affect bone metabolism (bisphosphonates, sodium fluoride, calcitonin, estroprogestins or anabolic steroids, corticosteroids, calcium or vitamin D, phosphate, thiazide diuretics) or drugs that interfere with contraceptive steroids (barbiturates, antiepileptics, rifampicin, griseofulvin), contraindications for the use of hormonal contraceptives
Interventions	1) Contraceptive patch delivering norelgestromin 150 µg plus EE 20 µg daily versus 2) Vaginal ring releasing etonogestrel 120 µg plus EE 15 µg daily Duration: 12 months
Outcomes	Bone mineral density by DEXA of lumbar spine (L1 to L4) Bone formation: serum osteocalcin; bone resorption: urinary pyridinoline and deoxypyridinoline.
Notes	Results for bone formation and resorption were presented in figures. On request, the investigator provided means, standard deviations, and Ns for analysis.

Massaro 2010 *(Continued)*

	Study was supported by institutional funds from investigators' university department

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	Blood and urine samples analyzed in laboratory blinded to treatment group; absorptiometry performed by blinded assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow chart provided. Losses due to drop-outs were 20% in each group; reasons for discontinuation were personal, irregular bleeding, and reaction to patch. No losses to follow up mentioned.

Naessen 1995

Methods	Randomized trial in Uppsala, Sweden.
Participants	22 women, 20 to 45 years, seeking contraceptive advice at family planning clinic, University Hospital.
Interventions	1) Levonorgestrel implant (Norplant) versus 2) DMPA 150 mg every 12 weeks Study duration: 6 months
Outcomes	Bone density in distal forearm by single photon absorptiometry. Bone density results shown in figure; no absolute numbers for variance. Serum calcium, alkaline phosphatase, and osteocalcin; urinary hydroxyproline/creatinine.
Notes	Investigator was unable to retrieve the BMD means and SD; publication was > 10 years old.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to the investigator, randomization procedure was a 'computer-based randomization.'
Allocation concealment (selection bias)	Low risk	Sealed envelopes were opened after inclusion of each subject.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information; interventions differed (injection versus implant)
Incomplete outcome data (attrition bias) All outcomes	Low risk	19/22 women completed the 6-month follow up; bone density measured in 18 (18% loss).

Nappi 2003

Methods	Randomized trial
Participants	40 healthy women desiring contraception. Inclusion criteria: 22 to 34 years old, age of menarche 12 to 14 years, ovulation in pretreatment cycle, BMI > 20 and < 22, normal menstrual cycles, normal diet without high or low calories. Exclusion criteria: pregnancy or breastfeeding in past year, liver disease, vascular or metabolic disorder, bone disease or disorder, smoking >10 cigarettes/day, migraine with aura, drugs that affect bone metabolism or with steroidal contraceptives, hysterectomy or oophorectomy, other contraindications for COCs.
Interventions	1) Ethinyl estradiol 20 µg plus gestodene 75 µg OC (FEDRA, Schering; Milan, Italy) (N=20) versus 2) Ethinyl estradiol 15 µg plus gestodene 60 µg OC (ARIANNA, Schering; Milan, Italy) (N=20) Study duration 1 year
Outcomes	BMD by DEXA at posterior-anterior lumbar spine (L1 to L4) Serum osteocalcin, urinary pyridinoline and deoxypyridinoline
Notes	Results shown in figures without absolute values. Unable to obtain further information from the investigator.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss: 8%; 3/40 women dropped out or missed the follow-up visit

Nappi 2005

Methods	Randomized controlled trial in Naples, Italy
Participants	48 healthy women in family planning clinic. Inclusion criteria: 22 to 34 years old, age of menarche 12 to 14 years, ovulation in pretreatment cycle, normal menstrual cycles, no abnormal dietary requirements. Exclusion criteria: pregnancy or breastfeeding in past year, liver disease, vascular or metabolic disorder, bone disease or disorder, smoke >= 10 cigarettes/day, migraine with aura, drugs that affect bone metabolism, drugs that interfere with steroidal contraceptives, hysterectomy or oophorectomy, other contraindications for COCs.
Interventions	1) Ethinyl estradiol 30 µg and drospirenone 3 mg OC (Yasmin; Schering, Milan, Italy) (N=24) versus 2) Ethinyl estradiol 30 µg and gestodene 75 µg OC (Ginoden; Schering) (N=24)

Nappi 2005 *(Continued)*

	Study duration 1 year
Outcomes	BMD by DEXA at posterior-anterior lumbar spine (L1 to L4). Serum and urinary calcium, serum osteocalcin, urinary pyridinoline and deoxypyridinoline. Results for biochemical measures shown in figures without absolute numbers.
Notes	Unable to obtain further information from investigator.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	Sequence was 'concealed both to researchers and patients until treatments were assigned.'
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss: 6%; 3/48 women dropped out.

Paoletti 2000

Methods	Randomized trial
Participants	20 healthy women desiring contraception. Inclusion criteria: 22 to 30 years old, normal menstrual cycles, age of menarche 12 to 14 years, BMI > 20 and < 22, no bone disease or disorder of bone metabolism, normal diet without low or high calories.
Interventions	1) Ethinyl estradiol 20 µg plus gestodene 75 µg OC versus 2) ethinyl estradiol 30 µg plus gestodene 75 µg OC. Each group had 10 women, according to communication from investigator. Study duration 12 months
Outcomes	Serum osteocalcin, urinary pyridinoline and deoxypyridinoline.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information

Paoletti 2000 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Study not blinded, according to author.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Report does not mention loss or discontinuation. Investigator communicated that all participants were included in the final analysis.

Rad 2011

Methods	Randomized multicenter trial conducted 2003-04; 2 sites in Netherlands and 2 sites in Poland Report is from a sub-study within larger trial (Teichmann 2009). Sample size of 50 per group based on 90% power to detect a difference of 0.458 mmol/l in total cholesterol values between treatment groups
Participants	147 healthy females. Inclusion criteria: 18 to 49 years old, body mass index 16 to 30 kg/m^2 (inclusive), regular menstrual cycle, and no contraindications for contraceptive steroids; willing to rely on study medication as only method of contraception. Exclusion criteria: diabetes; smoke <10 cigarettes daily; use of anticoagulant drugs, aspirin, lipid-lowering drugs, or drugs that would compromise contraceptive effect of COCs
Interventions	1) Continuous regimen of COC containing LNG 90 µg plus EE 20 µg versus 2) Cyclic regimen (21 days on, 7 days off) of COC containing LNG 100 µg and EE 20 µg Duration: 1 year
Outcomes	Bone markers were C-telopeptide and osteocalcin. Other metabolic measures included carbohydrate, lipid, and hemostatic variables.
Notes	Data insufficient for analysis: standard errors reported without sample sizes. Unable to obtain additional information from investigator. Study was sponsored by Wyeth (acquired by Pfizer in Oct 2009); 6 investigators received sponsor support for study and analysis and the other 2 were sponsor employees.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Interactive voice-recognition system
Allocation concealment (selection bias)	Low risk	Interactive voice-recognition system
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses other than discontinuations: 7% overall; continuous regimen 8% (6/74) and cyclic regimen 5% (4/73)

Rad 2011 *(Continued)*

	Losses total: 29% overall; continuous regimen 34% (25/74) and cyclic regimen 23% (17/73) Excluded from analysis participants with: a) only baseline values and b) outlying on-treatment values (mean ± 3 SD; determined in blinded fashion).

Sordal 2012

Methods	Randomized trial, conducted in Norway from Sep 2006 to Jun 2009. Sample size based on change in z-scores of BMD of lumbar spine and femoral neck after 2 years. Based on variability in recent BMD studies, 55 women in each group, with 35% drop-out rate, would provide 80% power to detect 0.20 to 0.34 difference.
Participants	110 healthy women, 20 to 35 years old, from one gynecology center. Inclusion criteria: sexually active women, at risk for pregnancy and not planning to use condoms during treatment; 20 to 35 years of age at screening; body mass index of 17 to 35 kg/m^2; good physical and mental health. Exclusion criteria: family history of osteoporotic fracture < age of 70; postgastrectomy; history of eating disorder; endocrine disorder (including controlled diabetes, [para]thyroid disease, Cushing's disease); rheumatoid arthritis; significant scoliosis; laboratory results outside reference range for fasting parathyroid hormone (PTH), fasting calcitonin, prolactin (hyperprolactinemia), fasting cholesterol or triglycerides (above range for age or treatment with lipid lowering drugs); engaging in vigorous exercise such as marathon, competitive swimming, triathlon; smoking > 10 cigarettes per day; > two units of alcohol a day; use of gonadotropin releasing hormone analogues, corticosteroids, thiazide diuretics, thyroid hormone, bisphosphonates, calcium with vitamin D supplementation; treatment after childhood with fluorides; contraindications for contraceptive steroids; abnormal cervical smear at screening; use of injectable hormonal contraception; pregnancy or breastfeeding in past 12 months; use in past 2 months of phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, ketoconazole, sex steroids (other than pre- and post-treatment contraceptive method) and herbal remedies containing Hypericum perforatum (St John's Wort); other investigational drug or trial participation in past 2 months.
Interventions	1) Nomegestrol 2.5 mg plus [17ß] estradiol 1.5 mg (NOMAC-E2) (24/4 day regimen) versus 2) Levonorgestrel 150 µg plus ethinyl estradiol 30 µg (LNG/EE) (21/7 day regimen) Duration: 2 years
Outcomes	Bone mineral density by DEXA: mean change in z-score of lumbar spine (L2 to L4) and femoral neck. Cell sizes for analysis obtained from ClinicalTrials.gov posting. z-score = (BMD - mean for age-matched reference population)/ SD for age-matched reference population
Notes	Listed as Schering-Plough 2011 in the previous update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no information
Allocation concealment (selection bias)	Unclear risk	no information

Sordal 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow up: NOMAC-E2, 2% (1/56), LNG/EE, 9% (5/54). Total losses: NOMAC-E2, 23% (13/56); LNG/EE, 41% (22/54).

Von Kesseru 2000

Methods	Randomized controlled trial in Argentina
Participants	148 healthy women, 38 to 50 years old, requesting contraception in 6 family planning centers. Inclusion criterion: normal menstrual patterns. Exclusion criteria: FSH < 40 IU, total cholesterol > 240 mg/dl, total triglycerides > 250 mg/dl, high-density lipoprotein cholesterol < 35 mg/dl, low-density lipoprotein cholesterol > 160 mg/dl.
Interventions	1) Monthly injections of norethisterone enanthate 50 mg plus estradiol valerate 5 mg (Mesigyna) (N=49). The first injection was given within first 5 days of first treatment cycle. 2) Nova-T IUD (N=99). IUD was fitted within first 5 days of cycle. Study duration was 24 months
Outcomes	BMD of lumbar spine with DEXA was a secondary outcome; half the women had bone density measures. Primary study outcome was measurement of lipids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random list used to allocate 1:2. According to the author, allocation was from a randomized table provided by Schering.
Allocation concealment (selection bias)	Unclear risk	Co-author could not provide information on allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses were high from the half allocated to bone density measures: for 12-month change, 48% Mesigyna and 79% IUD; for 24-month change, 70% and 84%, respectively.

BMD = bone mineral density
DEXA = dual-energy X-ray absorptiometry
DMPA = depot medroxyprogesterone acetate; Depo-Provera
FSH = follicle stimulating hormone
OC = oral contraceptive; COC = combination oral contraceptive

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

Study	Reason for exclusion
Berenson 2012	Not RCT; women chose contraceptive method.
Carr 2003	Participants were being treated for either uterine leiomyomata or endometriosis.
Gai 2011	No mention of randomization
Gambacciani 2006	Perimenopausal women recruited from Menopause Clinic. Comparison groups were not clearly reported.
Hauser 1970	Study was identified in CENTRAL search, but bone health was not an outcome.
Lattakova 2009	Not a randomized study. Participants were assigned numbers; even numbers were for the gestodene COC and odd numbers for the drospirenone COC.
Pfizer 2008	Non-randomized study, according to company report. Information on ClinicalTrials.gov was inconsistent, listing the study as randomized while the description stated the comparison would be a group electing non-hormonal contraception or abstinence.
Pinter 2003	Study was not RCT, according to correspondence with the investigator.
Shuzhi 2000	English translation of abstract included the word 'randomly'. Article, written in Chinese, had no mention of randomization. In this convenient cohort study, groups were based on willingness to use DMPA or condoms.
Teegarden 2005	Intervention was dietary counseling regarding calcium intake; groups were stratified by OC use or non-use.

OC = oral contraceptive

Characteristics of studies awaiting assessment *[ordered by study ID]*

Teva 2013

Methods	Randomized trial
Participants	1363 adolescent females seeking contraception Inclusion criteria: healthy postmenarchal adolescent female 12-18 years old, non-pregnant, non-lactating, regular menstrual cycles, BMI: 18 kg/m^2 to <30 kg/m^2, weight < 200 lbs, others as dictated by FDA-approved protocol Exclusion criteria: contraindication to use of oral contraceptives, history of clinically significant adverse event while taking hormonal contraceptives, use of medication which could significantly interfere with study assessments, others as dictated by FDA-approved protocol.
Interventions	1) Levonorgestrel 150 µg plus ethinyl estradiol 30 µg and ethinyl estradiol 10 µg versus 2) levonorgestrel 100 µg plus ethinyl estradiol 20 µg and placebo Duration: 13 months
Outcomes	Primary: Mean percent change in lumbar spine BMD via dual energy x-ray absorptiometry (DXA)

Teva 2013 *(Continued)*

	Secondary: Absolute change in lumbar spine, proximal femur, and total body bone mineral density and bone mineral content (BMC) via DXA scan from baseline to month 6 and to month 12; effects on biochemical markers of bone resorption and bone formation; safety and tolerability of DR-105
Notes	Completion date: Oct 2012; no report found and no results posted. ClinicalTrials.gov last updated 10 Apr 2013. Listed as Duramed 2011 in previous update. Control group (not seeking contraception) not randomized.

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

Bonny 2013

Trial name or title	Drug Exposure and Depot Medroxyprogesterone Acetate (DMPA) in Adolescent Subjects
Methods	Randomized controlled trial, open-label, conducted at a hospital in Columbus, Ohio (USA).
Participants	45 young women, age 12 to 21 years. Inclusion Criteria: 12 to 21 years old, healthy, post-menarchal, self-selected to use DMPA, willing to use barrier method of contraception in addition to DMPA. Exclusion criteria: 1. Chronic disease known to affect weight or BMD (e.g. diabetes, kidney) 2. Use of medication known to affect weight or BMD (e.g. corticosteroids) 3. DMPA use in past 12 months 4. Pregnancy in past 6 months 5. Etonogestrel implant, levonorgestrel-releasing intrauterine system or combination contraceptive use in past 30 days (OC, patch, vaginal ring) 6. Weight exceeding 450 lbs 7. Need for confidential contraceptive care for individuals < 18 years of age
Interventions	Depot medroxyprogesterone acetate (DMPA) intramuscular every 12 weeks for 12 months: 150 mg versus 104 mg versus 75 mg
Outcomes	Change in lumbar spine bone mineral density (BMD); change in total hip and femoral neck BMD. Duration: 48 weeks
Starting date	Sep 2011; estimated study completion, Dec 2014.
Contact information	Andrea Bonny, MD; Nationwide Children's Hospital
Notes	Purpose: to examine effect of different doses of DMPA on weight gain and BMD among adolescents.

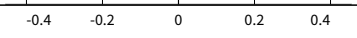
DATA AND ANALYSES

Comparison 1. Levonorgestrel-releasing implants: Norplant versus Chinese implant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density (L2 to L4) at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.02, 0.10]
2 Bone mineral density (femoral neck) at 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.11]
3 Bone mineral density (trochanter) at 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.08]
4 Bone mineral density (Ward's triangle) at 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.00, 0.14]
5 Serum osteocalcin at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.58, 0.90]
6 Serum alkaline phosphatase at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	1.94 [-13.29, 17.17]
7 Urine hydroxyproline/creatinine at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	1.70 [-2.86, 6.26]
8 Urine calcium/creatinine at 12 months	1	60	Mean Difference (IV, Fixed, 95% CI)	-20.12 [-44.01, 3.77]

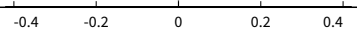
Analysis 1.1. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 1 Bone mineral density (L2 to L4) at 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Di 1999	29	1.1 (0.1)	31	1.1 (0.1)		100%	0.04[-0.02,0.1]
Total ***	**29**		**31**			**100%**	**0.04[-0.02,0.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.34(P=0.18)							

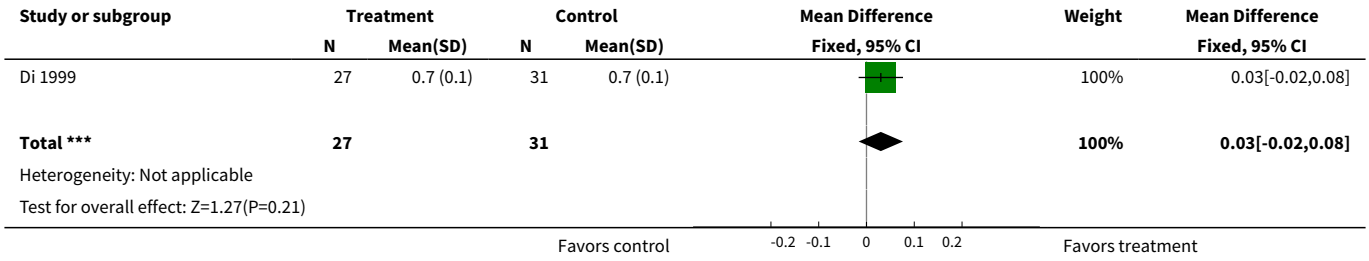


Analysis 1.2. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 2 Bone mineral density (femoral neck) at 12 months.

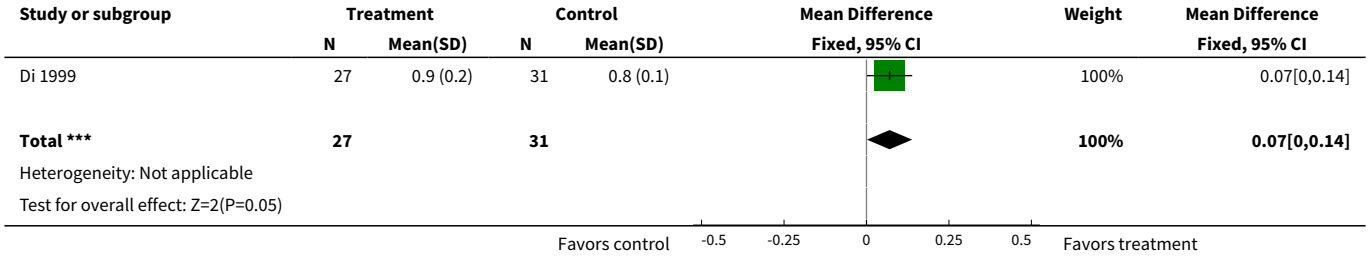
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Di 1999	27	0.9 (0.1)	31	0.8 (0.1)		100%	0.05[-0.01,0.11]
Total ***	**27**		**31**			**100%**	**0.05[-0.01,0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.68(P=0.09)							



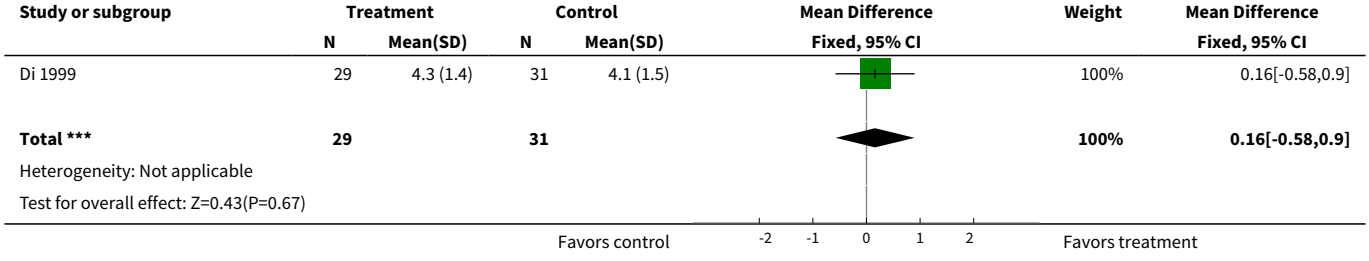
Analysis 1.3. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 3 Bone mineral density (trochanter) at 12 months.



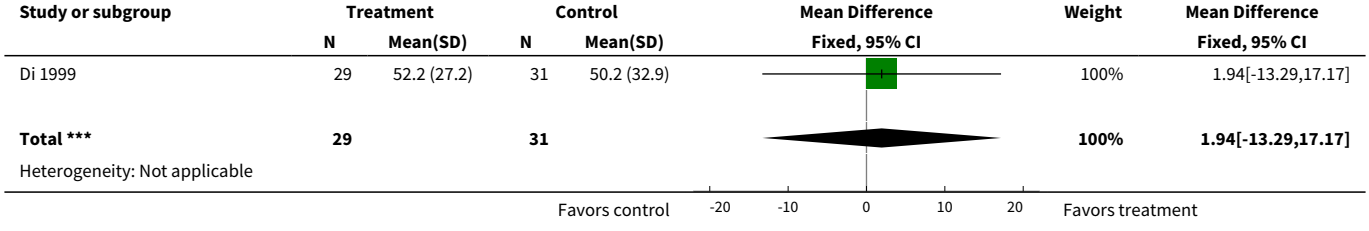
Analysis 1.4. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 4 Bone mineral density (Ward's triangle) at 12 months.

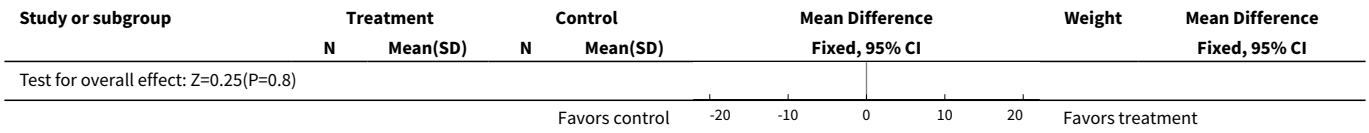


Analysis 1.5. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 5 Serum osteocalcin at 12 months.

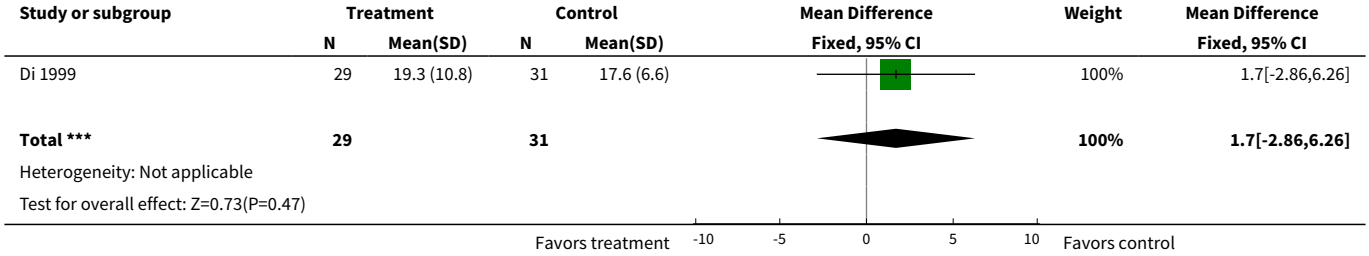


Analysis 1.6. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 6 Serum alkaline phosphatase at 12 months.

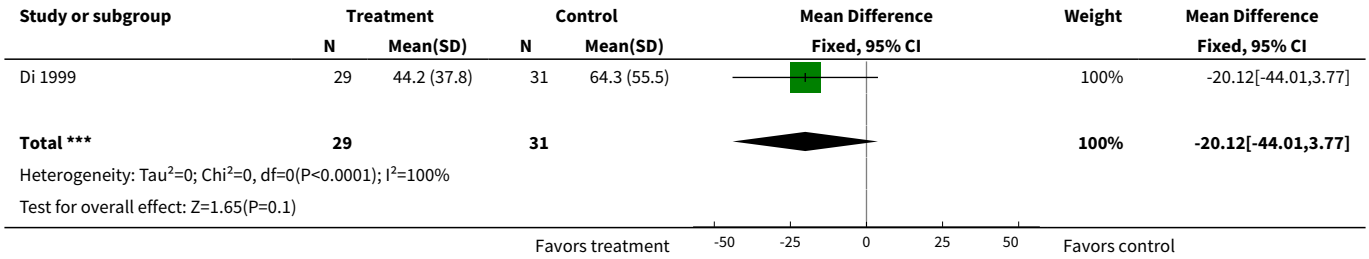




Analysis 1.7. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 7 Urine hydroxyproline/creatinine at 12 months.



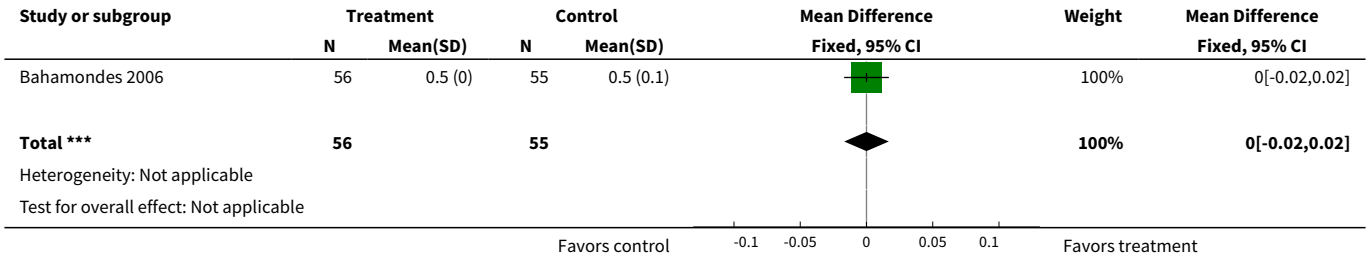
Analysis 1.8. Comparison 1 Levonorgestrel-releasing implants: Norplant versus Chinese implant, Outcome 8 Urine calcium/creatinine at 12 months.



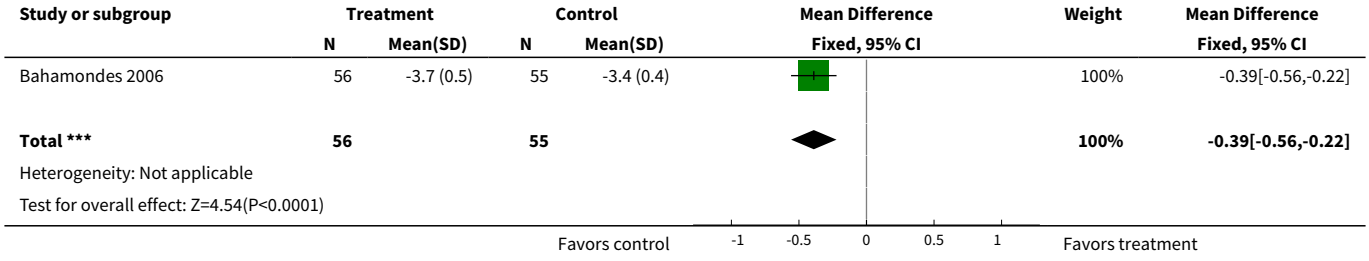
Comparison 2. Etonogestrel-releasing implant versus levonorgestrel-releasing implant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density (midshaft ulna) at 18 months	1	111	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.02, 0.02]
2 Percent change in bone mineral density (midshaft ulna) by 18 months	1	111	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.56, -0.22]
3 Bone mineral density (distal radius) at 18 months	1	111	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.02, 0.02]
4 Percent change in bone mineral density (distal radius) by 18 months	1	111	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.09, -0.91]
5 Bone mineral density (distal radius) at 36 months	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.02]

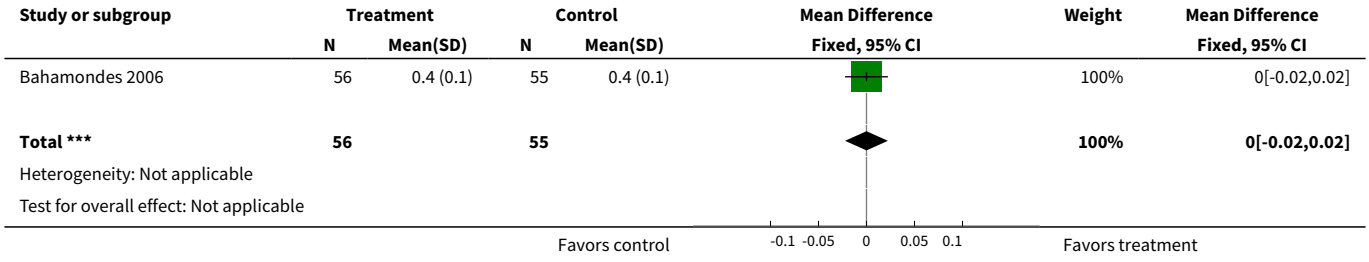
Analysis 2.1. Comparison 2 Etonogestrel-releasing implant versus levonorgestrel-releasing implant, Outcome 1 Bone mineral density (midshaft ulna) at 18 months.



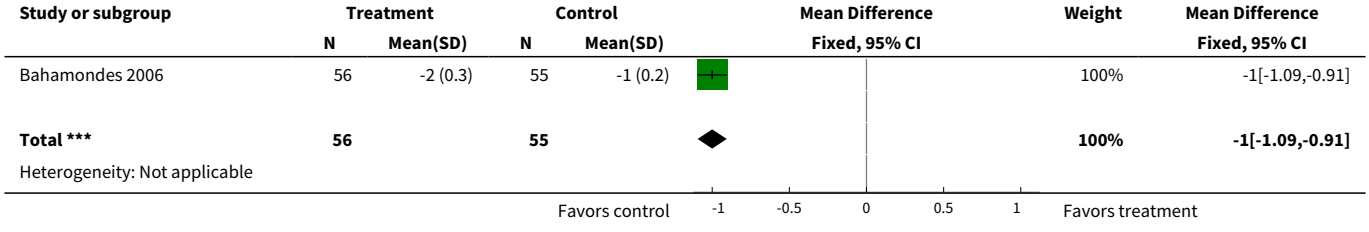
Analysis 2.2. Comparison 2 Etonogestrel-releasing implant versus levonorgestrel-releasing implant, Outcome 2 Percent change in bone mineral density (midshaft ulna) by 18 months.

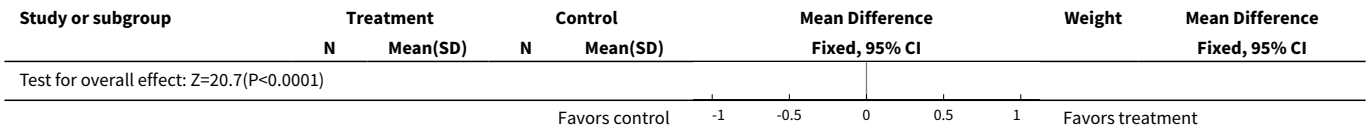


Analysis 2.3. Comparison 2 Etonogestrel-releasing implant versus levonorgestrel-releasing implant, Outcome 3 Bone mineral density (distal radius) at 18 months.

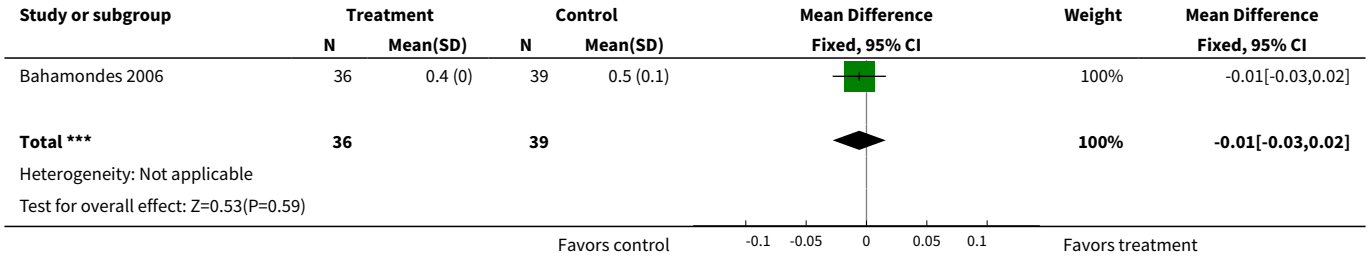


Analysis 2.4. Comparison 2 Etonogestrel-releasing implant versus levonorgestrel-releasing implant, Outcome 4 Percent change in bone mineral density (distal radius) by 18 months.





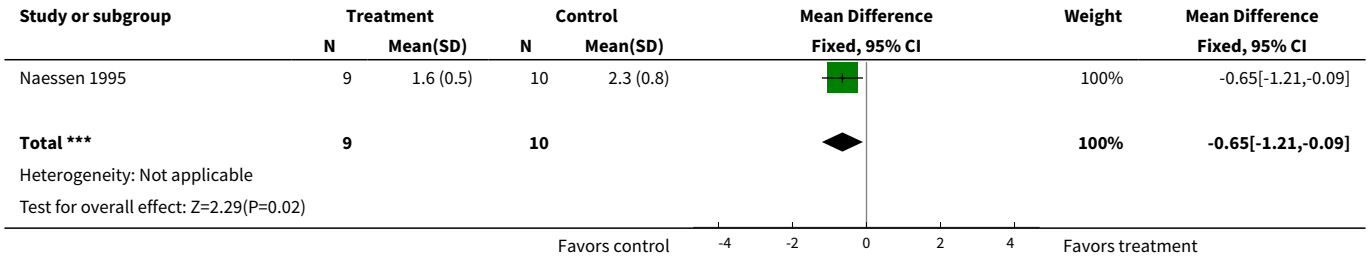
Analysis 2.5. Comparison 2 Etonogestrel-releasing implant versus levonorgestrel-releasing implant, Outcome 5 Bone mineral density (distal radius) at 36 months.



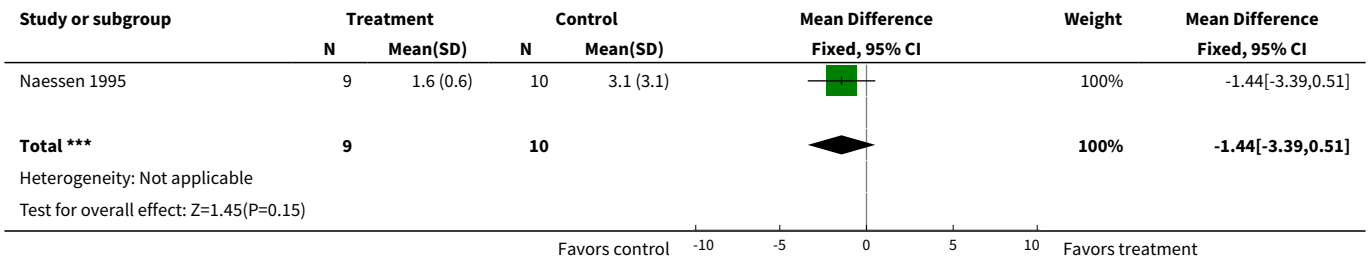
Comparison 3. DMPA 150 mg versus levonorgestrel-releasing implant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum alkaline phosphatase at 6 months	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.21, -0.09]
2 Serum osteocalcin at 6 months	1	19	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-3.39, 0.51]
3 Serum calcium at 6 months	1	19	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]
4 Urinary hydroxyproline/creatinine at 6 months	1	19	Mean Difference (IV, Fixed, 95% CI)	7.30 [-14.52, 29.12]

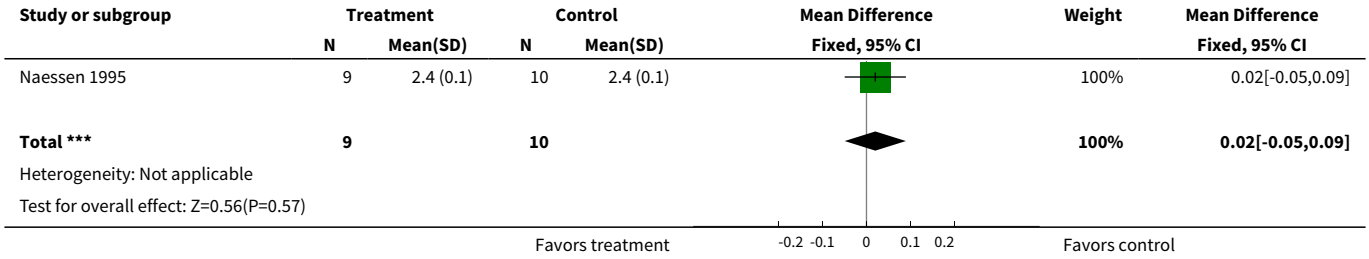
Analysis 3.1. Comparison 3 DMPA 150 mg versus levonorgestrel-releasing implant, Outcome 1 Serum alkaline phosphatase at 6 months.



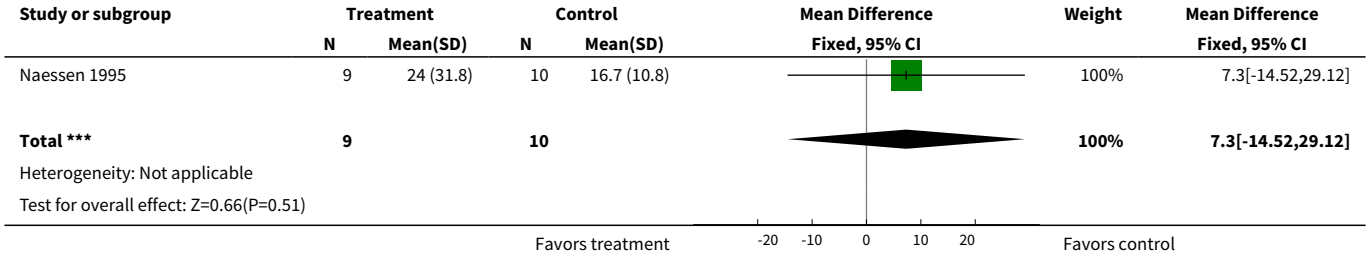
Analysis 3.2. Comparison 3 DMPA 150 mg versus levonorgestrel-releasing implant, Outcome 2 Serum osteocalcin at 6 months.



Analysis 3.3. Comparison 3 DMPA 150 mg versus levonorgestrel-releasing implant, Outcome 3 Serum calcium at 6 months.



Analysis 3.4. Comparison 3 DMPA 150 mg versus levonorgestrel-releasing implant, Outcome 4 Urinary hydroxyproline/creatinine at 6 months.



Comparison 4. DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percent change in bone mineral density (spine) by 12 months	1	69	Mean Difference (IV, Fixed, 95% CI)	2.90 [1.80, 4.00]
2 Percent change in bone mineral apparent density (spine) by 12 months	1	69	Mean Difference (IV, Fixed, 95% CI)	2.7 [1.60, 3.80]

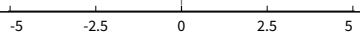
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Percent change in bone mineral density (femoral neck) by 12 months	1	69	Mean Difference (IV, Fixed, 95% CI)	3.2 [1.36, 5.04]
4 Percent change in bone mineral apparent density (femoral neck) by 12 months	1	69	Mean Difference (IV, Fixed, 95% CI)	1.2 [-2.01, 4.41]
5 Percent change in bone mineral density (spine) by 24 months	1	34	Mean Difference (IV, Fixed, 95% CI)	4.6 [2.87, 6.33]
6 Percent change in bone mineral apparent density (spine) by 24 months	1	34	Mean Difference (IV, Fixed, 95% CI)	4.9 [3.11, 6.69]
7 Percent change in bone mineral density (femoral neck) by 24 months	1	34	Mean Difference (IV, Fixed, 95% CI)	9.8 [4.96, 14.64]
8 Percent change in bone mineral apparent density (femoral neck) by 24 months	1	34	Mean Difference (IV, Fixed, 95% CI)	7.10 [0.50, 13.70]

Analysis 4.1. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 1 Percent change in bone mineral density (spine) by 12 months.

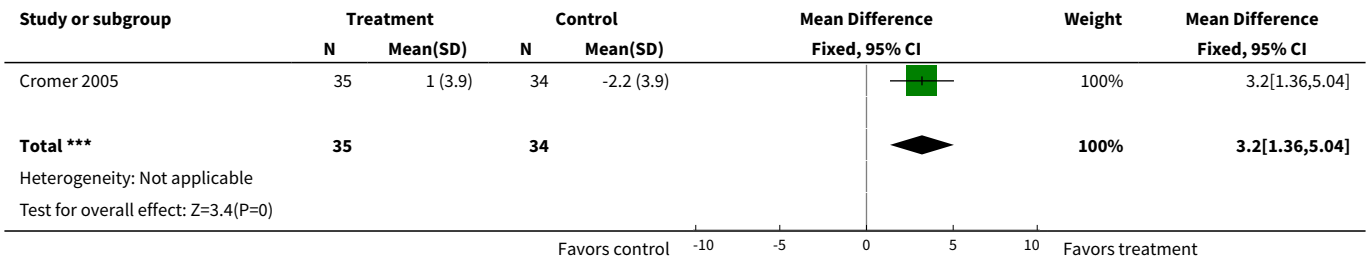
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cromer 2005	35	1.3 (2.3)	34	-1.6 (2.3)		100%	2.9[1.8,4]
Total ***	**35**		**34**			**100%**	**2.9[1.8,4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.19(P<0.0001)							

Analysis 4.2. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 2 Percent change in bone mineral apparent density (spine) by 12 months.

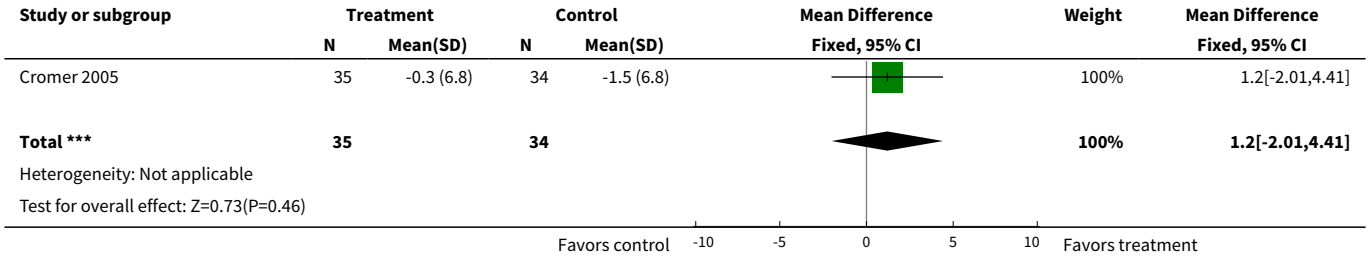
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cromer 2005	35	1.2 (2.3)	34	-1.5 (2.3)		100%	2.7[1.6,3.8]
Total ***	**35**		**34**			**100%**	**2.7[1.6,3.8]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.83(P<0.0001)							



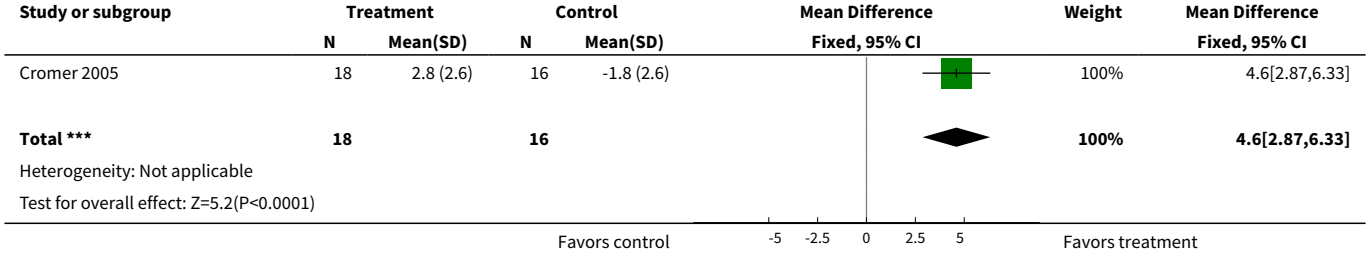
Analysis 4.3. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 3 Percent change in bone mineral density (femoral neck) by 12 months.



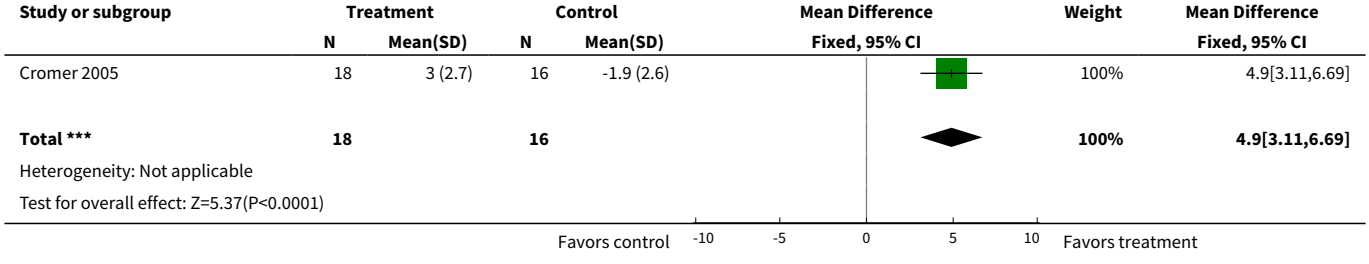
Analysis 4.4. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 4 Percent change in bone mineral apparent density (femoral neck) by 12 months.



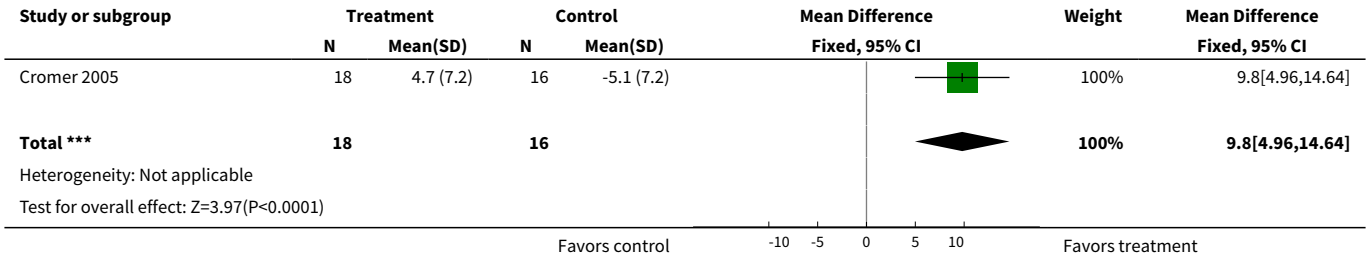
Analysis 4.5. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 5 Percent change in bone mineral density (spine) by 24 months.



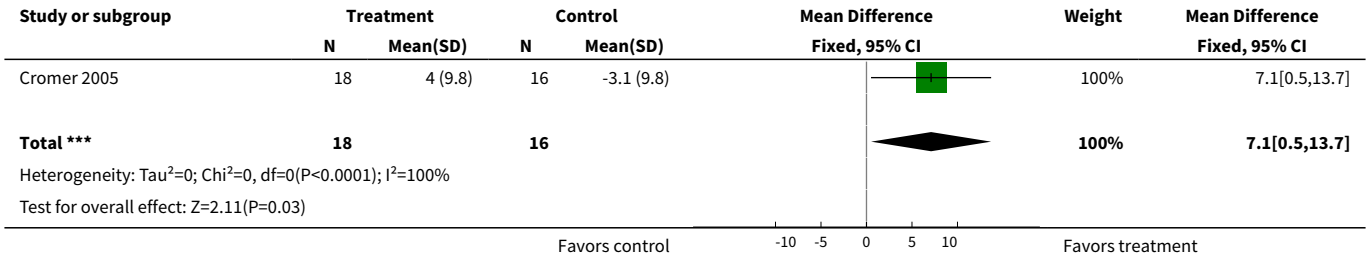
Analysis 4.6. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 6 Percent change in bone mineral apparent density (spine) by 24 months.



Analysis 4.7. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 7 Percent change in bone mineral density (femoral neck) by 24 months.



Analysis 4.8. Comparison 4 DMPA 150 mg + estradiol cypionate 5 mg versus DMPA 150 mg + placebo, Outcome 8 Percent change in bone mineral apparent density (femoral neck) by 24 months.

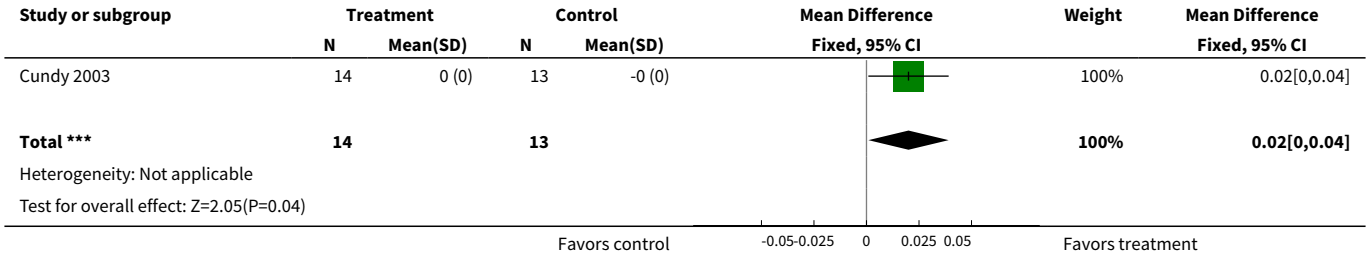


Comparison 5. DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo

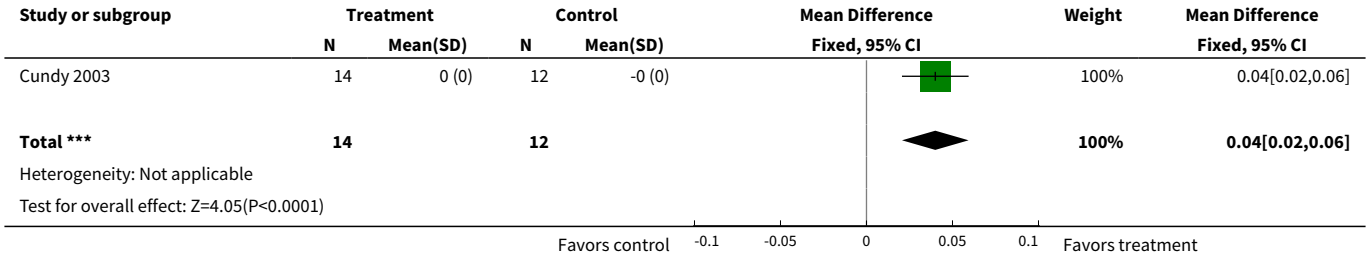
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in bone mineral density (lumbar spine) by 12 months	1	27	Mean Difference (IV, Fixed, 95% CI)	0.02 [0.00, 0.04]
2 Change in bone mineral density (lumbar spine) by 24 months	1	26	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.02, 0.06]
3 Change in bone mineral density (Ward's triangle) by 12 months	1	26	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]
4 Change in bone mineral density (Ward's triangle) by 24 months	1	25	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.00, 0.08]
5 Change in bone mineral density (trochanter) by 12 months	1	26	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.01, 0.07]
6 Change in bone mineral density (trochanter) by 24 months	1	25	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.05]
7 Change in bone mineral density (femoral neck) by 12 months	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.04, 0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Change in bone mineral density (femoral neck) by 24 months	1	26	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.02, 0.06]
9 Change in bone mineral density (total body) by12 months	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
10 Change in bone mineral density (total body) by 24 months	1	26	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.03]

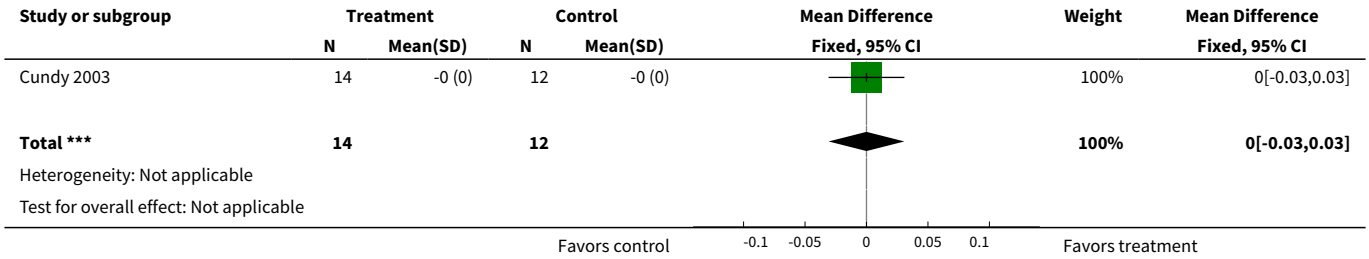
Analysis 5.1. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 1 Change in bone mineral density (lumbar spine) by 12 months.



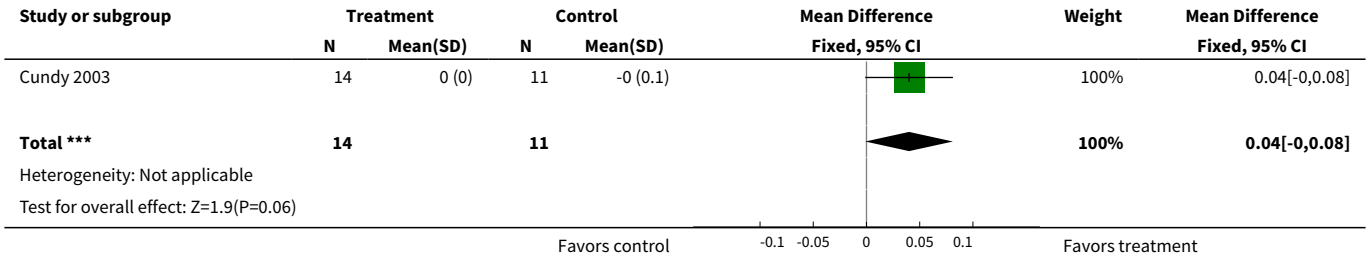
Analysis 5.2. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 2 Change in bone mineral density (lumbar spine) by 24 months.



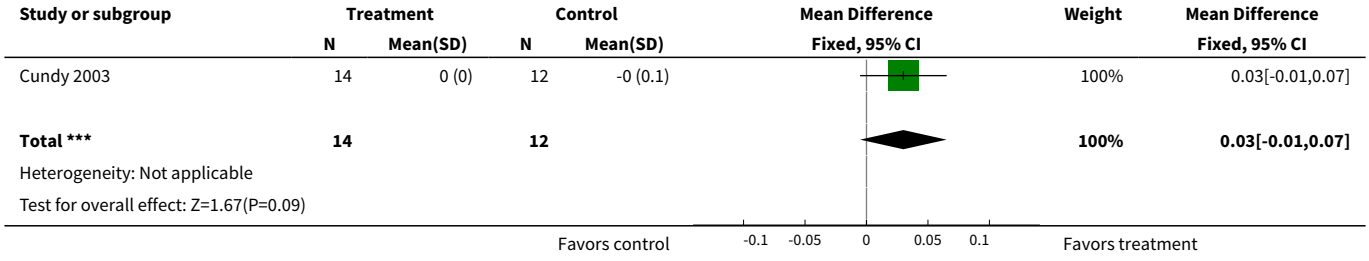
Analysis 5.3. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 3 Change in bone mineral density (Ward's triangle) by 12 months.



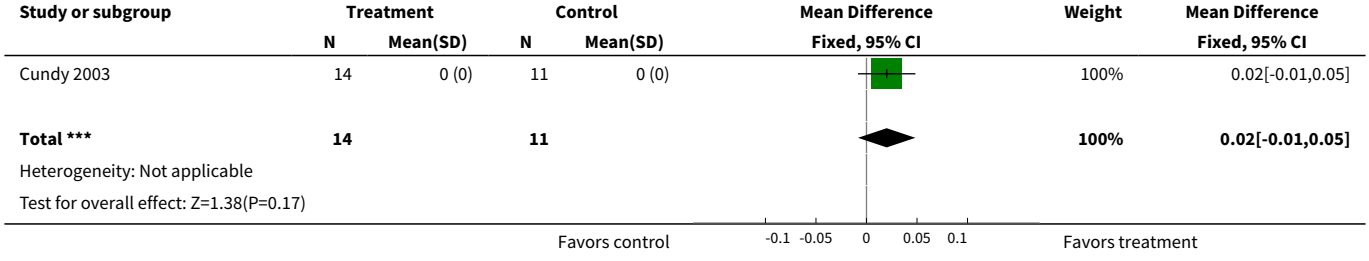
Analysis 5.4. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 4 Change in bone mineral density (Ward's triangle) by 24 months.



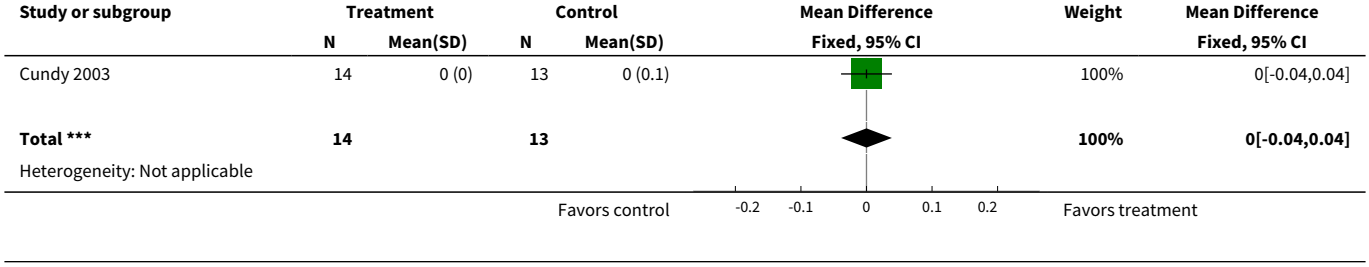
Analysis 5.5. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 5 Change in bone mineral density (trochanter) by 12 months.



Analysis 5.6. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 6 Change in bone mineral density (trochanter) by 24 months.



Analysis 5.7. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 7 Change in bone mineral density (femoral neck) by 12 months.



Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Not applicable							

Favors control | Favors treatment

Analysis 5.8. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 8 Change in bone mineral density (femoral neck) by 24 months.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cundy 2003	14	0 (0.1)	12	-0 (0.1)		100%	0.02[-0.02,0.06]
Total ***	**14**		**12**			**100%**	**0.02[-0.02,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							

Favors control | Favors treatment

Analysis 5.9. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 9 Change in bone mineral density (total body) by12 months.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cundy 2003	14	0 (0)	13	0 (0)		100%	0[-0.01,0.01]
Total ***	**14**		**13**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favors control | Favors treatment

Analysis 5.10. Comparison 5 DMPA 150 mg + conjugated estrogens 625 µg versus DMPA 150 mg + placebo, Outcome 10 Change in bone mineral density (total body) by 24 months.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cundy 2003	14	0 (0)	12	0 (0)		100%	0.01[-0.01,0.03]
Total ***	**14**		**12**			**100%**	**0.01[-0.01,0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.27(P=0.2)							

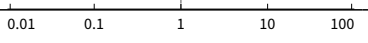
Favors control | Favors treatment

Comparison 6. DMPA-SC 104 mg versus DMPA-IM 150 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in total hip BMD >= 5% from baseline (year 1)	1	328	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.26]
2 Decrease in total hip BMD >= 5% from baseline (year 2)	1	207	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.40]
3 Decrease in total hip BMD >= 5% from baseline (year 3)	1	117	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.56, 2.41]
4 Decrease in lumbar spine BMD >= 5% from baseline (year 1)	1	328	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.32]
5 Decrease in lumbar spine BMD >= 5% from baseline (year 2)	1	208	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 1.01]
6 Decrease in lumbar spine BMD >= 5% from baseline (year 3)	1	115	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [1.00, 4.45]

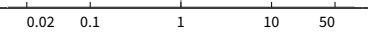
Analysis 6.1. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 1 Decrease in total hip BMD >= 5% from baseline (year 1).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	13/166	20/162		100%	0.6[0.29,1.26]
Total (95% CI)	**166**	**162**		**100%**	**0.6[0.29,1.26]**
Total events: 13 (Experimental), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.35(P=0.18)					



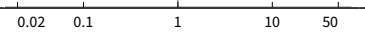
Analysis 6.2. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 2 Decrease in total hip BMD >= 5% from baseline (year 2).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	30/106	34/101		100%	0.78[0.43,1.4]
Total (95% CI)	**106**	**101**		**100%**	**0.78[0.43,1.4]**
Total events: 30 (Experimental), 34 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.4)					



Analysis 6.3. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 3 Decrease in total hip BMD >= 5% from baseline (year 3).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	35/63	28/54		100%	1.16[0.56,2.41]
Total (95% CI)	**63**	**54**		**100%**	**1.16[0.56,2.41]**
Total events: 35 (Experimental), 28 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					



Analysis 6.4. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 4 Decrease in lumbar spine BMD >= 5% from baseline (year 1).

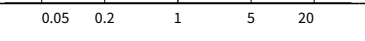
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	34/166	40/162		100%	0.79[0.47,1.32]
Total (95% CI)	**166**	**162**		**100%**	**0.79[0.47,1.32]**
Total events: 34 (Experimental), 40 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					

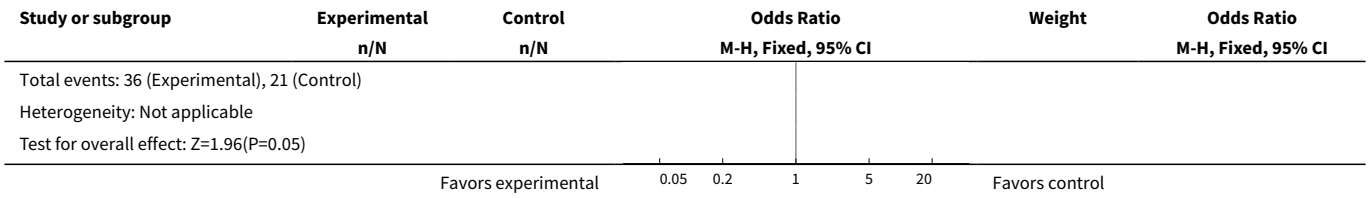
Analysis 6.5. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 5 Decrease in lumbar spine BMD >= 5% from baseline (year 2).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	40/106	52/102		100%	0.58[0.34,1.01]
Total (95% CI)	**106**	**102**		**100%**	**0.58[0.34,1.01]**
Total events: 40 (Experimental), 52 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.92(P=0.06)					

Analysis 6.6. Comparison 6 DMPA-SC 104 mg versus DMPA-IM 150 mg, Outcome 6 Decrease in lumbar spine BMD >= 5% from baseline (year 3).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Kaunitz 2009	36/62	21/53		100%	2.11[1,4.45]
Total (95% CI)	**62**	**53**		**100%**	**2.11[1,4.45]**

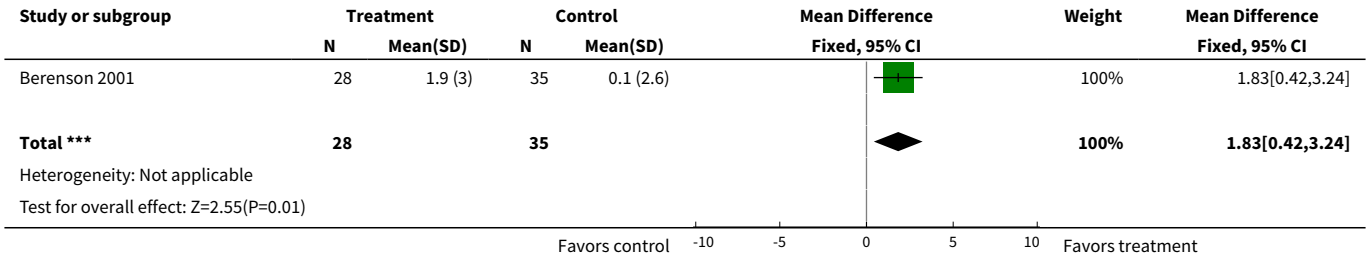




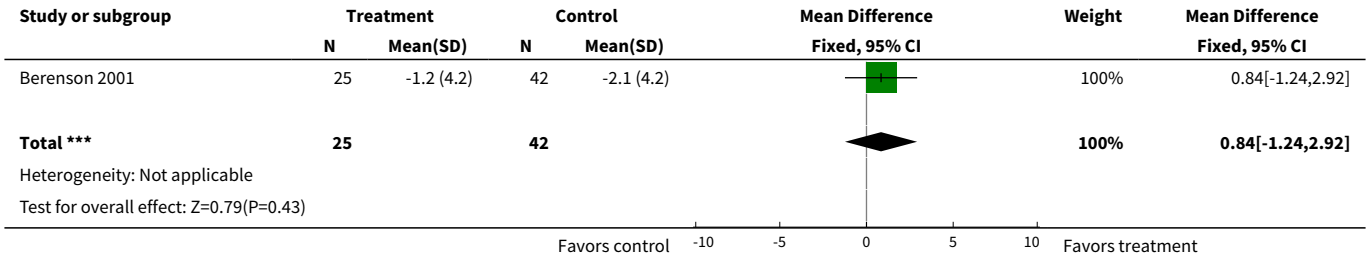
Comparison 7. Norethindrone 1 mg + EE 35 µg versus desogestrel 150 µg + EE 30 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percent change in bone mineral density (lumbar spine) by 12 months	1	63	Mean Difference (IV, Fixed, 95% CI)	1.83 [0.42, 3.24]
2 Percent change in bone mineral density (lumbar spine) by 24 months	1	67	Mean Difference (IV, Fixed, 95% CI)	0.84 [-1.24, 2.92]

Analysis 7.1. Comparison 7 Norethindrone 1 mg + EE 35 µg versus desogestrel 150 µg + EE 30 µg, Outcome 1 Percent change in bone mineral density (lumbar spine) by 12 months.



Analysis 7.2. Comparison 7 Norethindrone 1 mg + EE 35 µg versus desogestrel 150 µg + EE 30 µg, Outcome 2 Percent change in bone mineral density (lumbar spine) by 24 months.

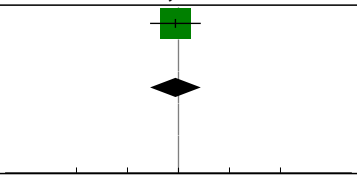


Comparison 8. Desogestrel 150 µg + EE 30 µg versus cyproterone acetate 2 mg + EE 35 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in BMD of lumbar spine by 12 months	1	277	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
2 Change in BMD of lumbar spine by 24 months	1	261	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
3 Change in BMD of femoral neck by 12 months	1	277	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.02, 0.02]
4 Change in BMD of femoral neck by 24 months	1	261	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.01]

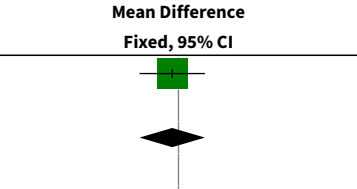
Analysis 8.1. Comparison 8 Desogestrel 150 µg + EE 30 µg versus cyproterone acetate 2 mg + EE 35 µg, Outcome 1 Change in BMD of lumbar spine by 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gai 2012	138	1 (0.1)	139	1 (0.1)		100%	-0[-0.03,0.02]
Total ***	**138**		**139**			**100%**	**-0[-0.03,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.24(P=0.81)							



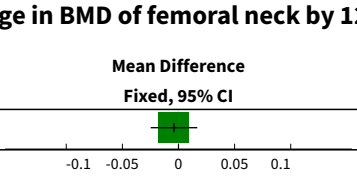
Analysis 8.2. Comparison 8 Desogestrel 150 µg + EE 30 µg versus cyproterone acetate 2 mg + EE 35 µg, Outcome 2 Change in BMD of lumbar spine by 24 months.

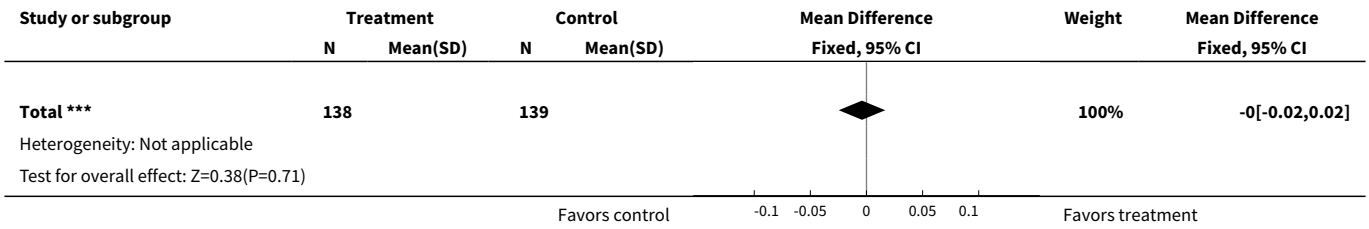
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gai 2012	127	1 (0.1)	134	1 (0.1)		100%	-0.01[-0.03,0.02]
Total ***	**127**		**134**			**100%**	**-0.01[-0.03,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.38(P=0.71)							



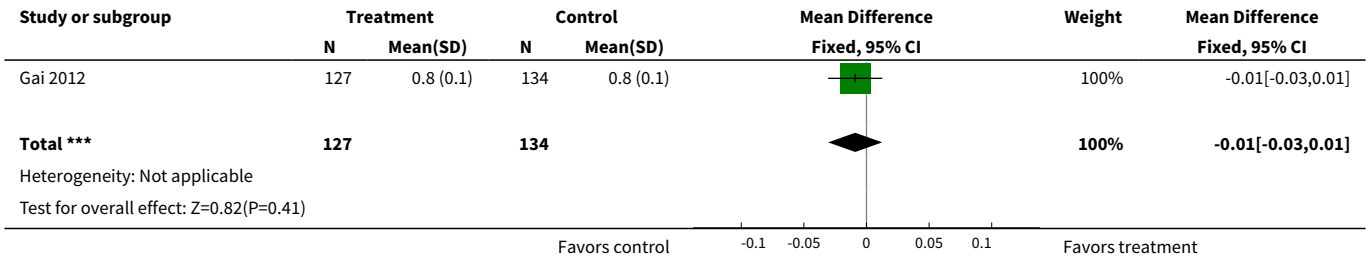
Analysis 8.3. Comparison 8 Desogestrel 150 µg + EE 30 µg versus cyproterone acetate 2 mg + EE 35 µg, Outcome 3 Change in BMD of femoral neck by 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gai 2012	138	0.8 (0.1)	139	0.8 (0.1)		100%	-0[-0.02,0.02]





Analysis 8.4. Comparison 8 Desogestrel 150 µg + EE 30 µg versus cyproterone acetate 2 mg + EE 35 µg, Outcome 4 Change in BMD of femoral neck by 24 months.

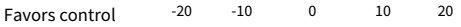


Comparison 9. Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density (lumbar spine) at 12 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-17.84, 13.64]
2 Bone mineral density (lumbar spine) at 24 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-18.29, 15.09]
3 Bone mineral density (lumbar spine) at 36 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.53 [-17.27, 10.21]
4 Percent change in bone mineral density (lumbar spine) by 36 months	1	39	Mean Difference (IV, Fixed, 95% CI)	0.40 [-3.00, 3.80]
5 Percent change in serum alkaline phosphatase (36 months)	1	39	Mean Difference (IV, Fixed, 95% CI)	-57.80 [-160.03, 44.43]
6 Percent change in cross-linked N-telopeptides (36 months)	1	39	Mean Difference (IV, Fixed, 95% CI)	-7.70 [-31.90, 16.50]

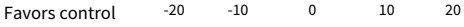
Analysis 9.1. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 1 Bone mineral density (lumbar spine) at 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Endrikat 2004	19	159.3 (26.9)	20	161.4 (23)		100%	-2.1[-17.84,13.64]
Total ***	**19**		**20**			**100%**	**-2.1[-17.84,13.64]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.79)							



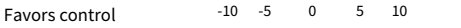
Analysis 9.2. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 2 Bone mineral density (lumbar spine) at 24 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Endrikat 2004	19	159.5 (29.3)	20	161.1 (23.4)		100%	-1.6[-18.29,15.09]
Total ***	**19**		**20**			**100%**	**-1.6[-18.29,15.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.19(P=0.85)							



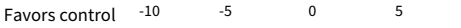
Analysis 9.3. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 3 Bone mineral density (lumbar spine) at 36 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Endrikat 2004	19	156.6 (20)	20	160.1 (23.7)		100%	-3.53[-17.27,10.21]
Total ***	**19**		**20**			**100%**	**-3.53[-17.27,10.21]**
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$							
Test for overall effect: Z=0.5(P=0.61)							

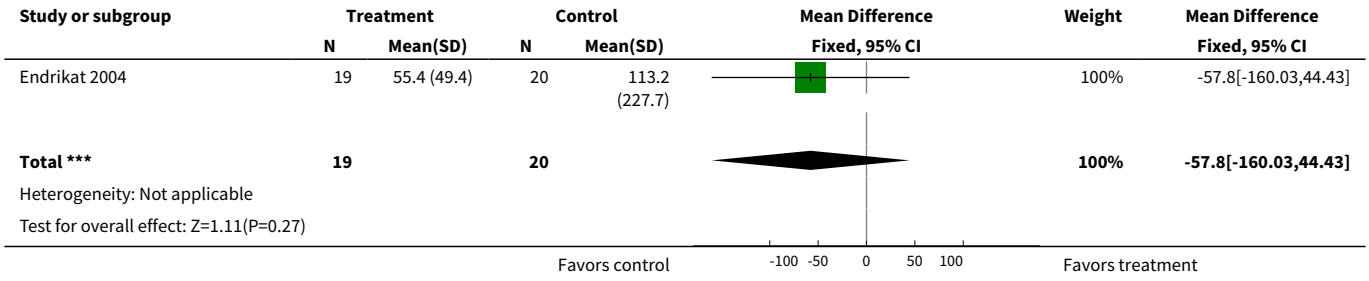


Analysis 9.4. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 4 Percent change in bone mineral density (lumbar spine) by 36 months.

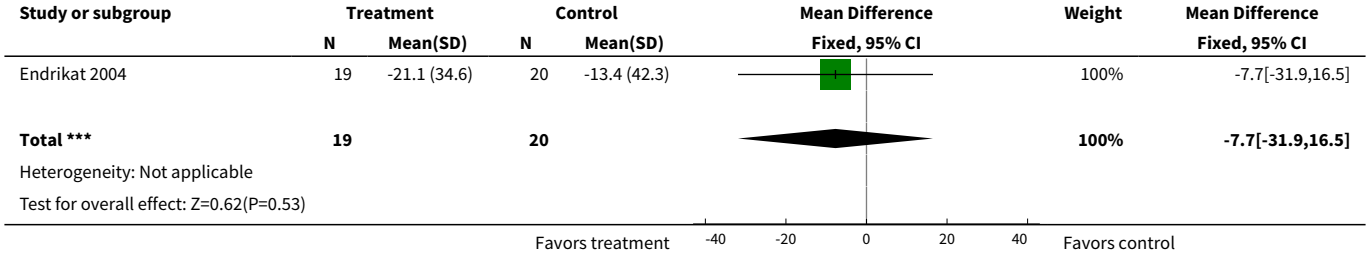
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Endrikat 2004	19	-0.4 (6.3)	20	-0.8 (4.3)		100%	0.4[-3,3.8]
Total ***	**19**		**20**			**100%**	**0.4[-3,3.8]**
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$							
Test for overall effect: Z=0.23(P=0.82)							



Analysis 9.5. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 5 Percent change in serum alkaline phosphatase (36 months).



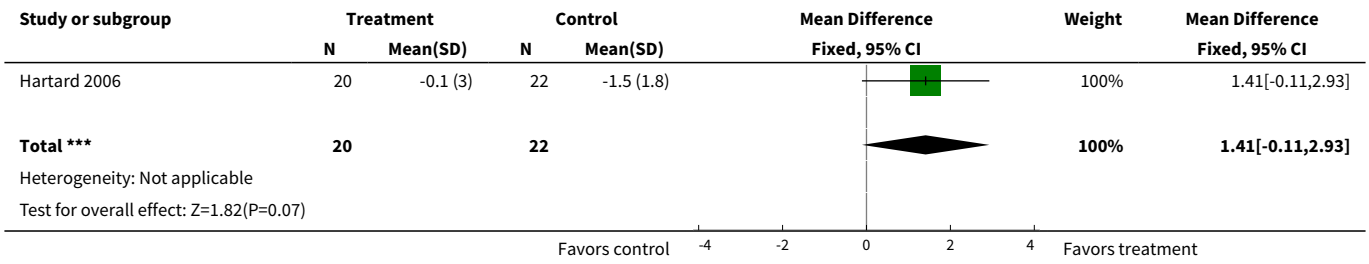
Analysis 9.6. Comparison 9 Levonorgestrel 100 µg + EE 20 µg versus levonorgestrel 150 µg + EE 30 µg, Outcome 6 Percent change in cross-linked N-telopeptides (36 months).



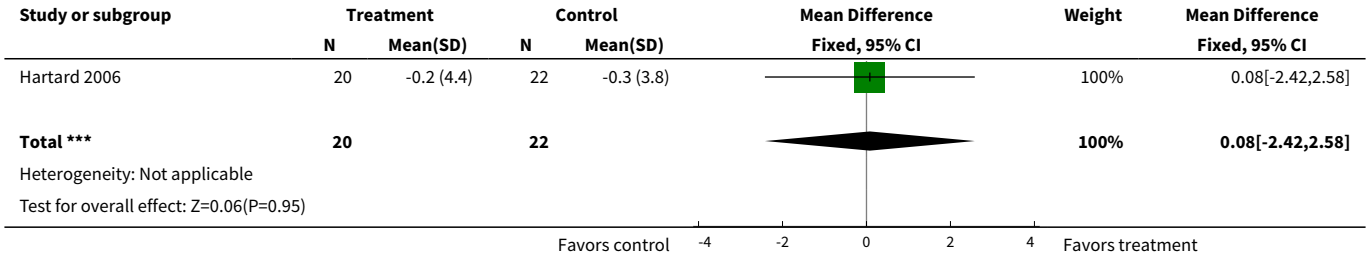
Comparison 10. Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percent change in areal bone mineral density (lumbar spine) by 12 months	1	42	Mean Difference (IV, Fixed, 95% CI)	1.41 [-0.11, 2.93]
2 Percent change in areal bone mineral density (femoral neck) by 12 months	1	42	Mean Difference (IV, Fixed, 95% CI)	0.08 [-2.42, 2.58]
3 Percent change in serum bone-specific alkaline phosphatase by 12 months	1	42	Mean Difference (IV, Fixed, 95% CI)	15.31 [3.91, 26.71]
4 Percent change in serum osteocalcin by 12 months	1	42	Mean Difference (IV, Fixed, 95% CI)	7.71 [-2.49, 17.91]
5 Percent change in serum cross-linked telopeptides by 12 months	1	42	Mean Difference (IV, Fixed, 95% CI)	16.39 [-8.41, 41.19]

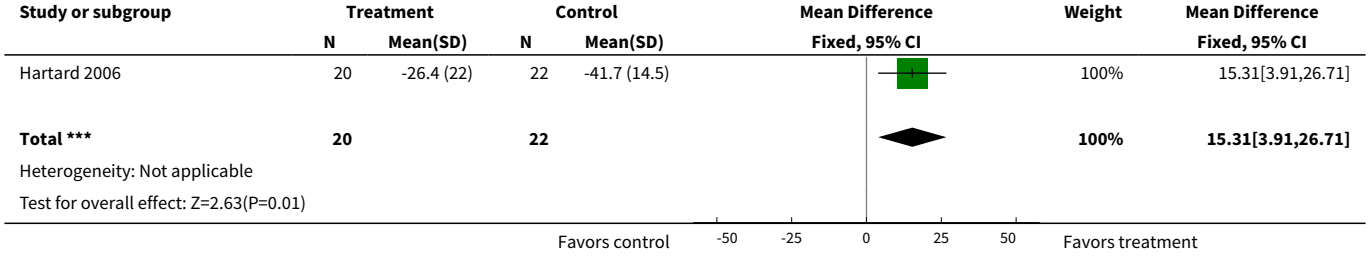
Analysis 10.1. Comparison 10 Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg, Outcome 1 Percent change in areal bone mineral density (lumbar spine) by 12 months.



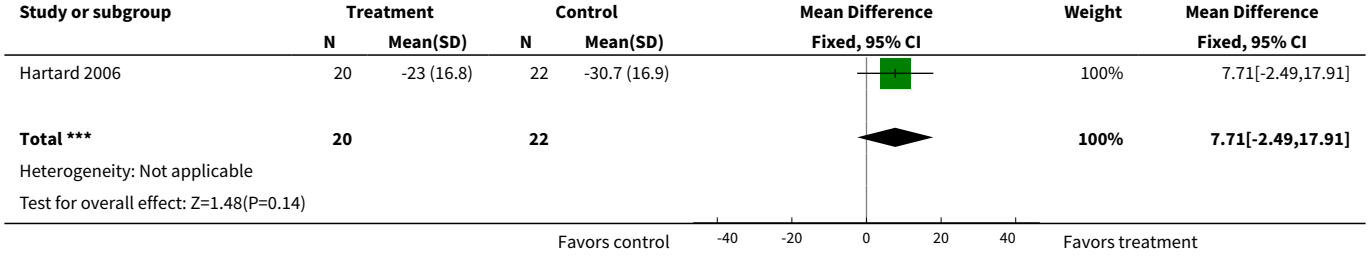
Analysis 10.2. Comparison 10 Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg, Outcome 2 Percent change in areal bone mineral density (femoral neck) by 12 months.



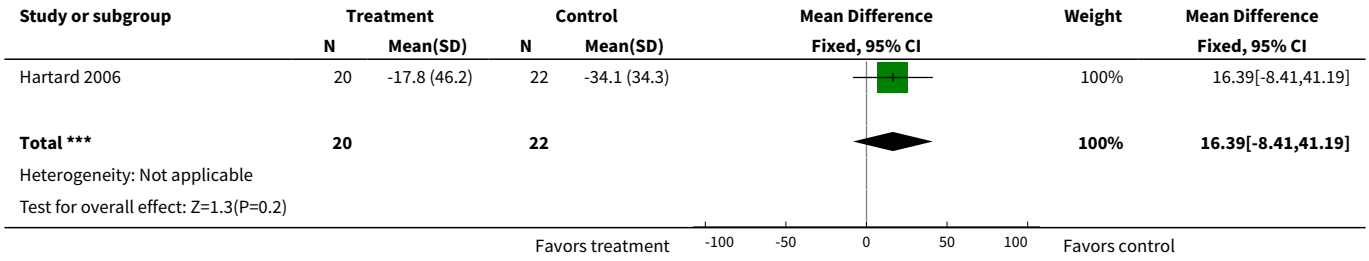
Analysis 10.3. Comparison 10 Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg, Outcome 3 Percent change in serum bone-specific alkaline phosphatase by 12 months.



Analysis 10.4. Comparison 10 Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg, Outcome 4 Percent change in serum osteocalcin by 12 months.



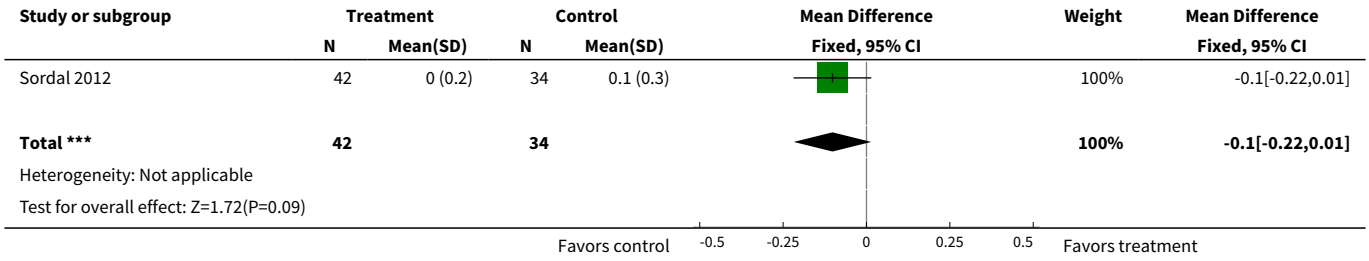
Analysis 10.5. Comparison 10 Levonorgestrel 100 µg + EE 20 µg versus desogestrel 150 µg + EE 20 µg, Outcome 5 Percent change in serum cross-linked telopeptides by 12 months.



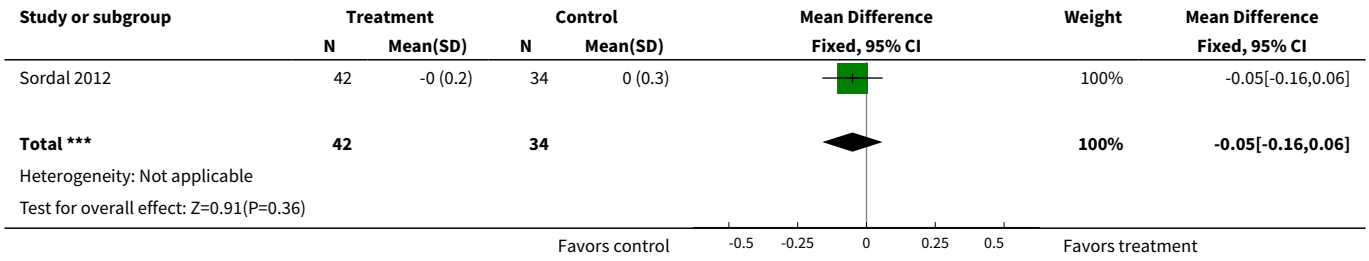
Comparison 11. Nomegestrol 2.5 mg + estradiol 1.5 mg versus levonorgestrel 150 µg + EE 30 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in z-score of lumbar spine after cycle 26	1	76	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.22, 0.01]
2 Change in z-score of femoral neck after cycle 26	1	76	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.16, 0.06]

Analysis 11.1. Comparison 11 Nomegestrol 2.5 mg + estradiol 1.5 mg versus levonorgestrel 150 µg + EE 30 µg, Outcome 1 Change in z-score of lumbar spine after cycle 26.



Analysis 11.2. Comparison 11 Nomegestrol 2.5 mg + estradiol 1.5 mg versus levonorgestrel 150 µg + EE 30 µg, Outcome 2 Change in z-score of femoral neck after cycle 26.

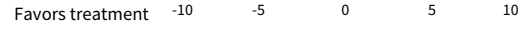


Comparison 12. Gestodene 75 µg + EE 20 µg versus gestodene 75 µg + EE 30 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary pyridinoline at 12 months	1	20	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.65, 2.05]
2 Urinary deoxypyridinoline at 12 months	1	20	Mean Difference (IV, Fixed, 95% CI)	1.20 [0.37, 2.03]
3 Serum osteocalcin at 12 months	1	20	Mean Difference (IV, Fixed, 95% CI)	1.60 [-1.87, 5.07]

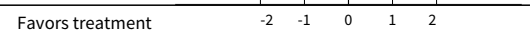
Analysis 12.1. Comparison 12 Gestodene 75 µg + EE 20 µg versus gestodene 75 µg + EE 30 µg, Outcome 1 Urinary pyridinoline at 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Paoletti 2000	10	32 (2.5)	10	31.8 (1.6)		100%	0.2[-1.65,2.05]
Total ***	**10**		**10**			**100%**	**0.2[-1.65,2.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							



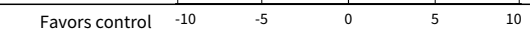
Analysis 12.2. Comparison 12 Gestodene 75 µg + EE 20 µg versus gestodene 75 µg + EE 30 µg, Outcome 2 Urinary deoxypyridinoline at 12 months.

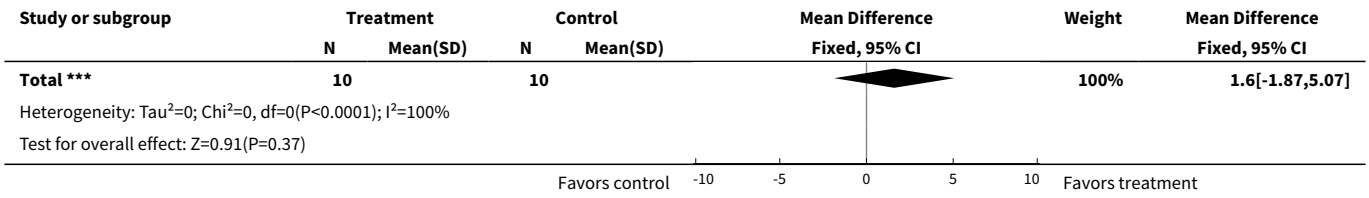
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Paoletti 2000	10	5.4 (1)	10	4.2 (1)		100%	1.2[0.37,2.03]
Total ***	**10**		**10**			**100%**	**1.2[0.37,2.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.82(P=0)							



Analysis 12.3. Comparison 12 Gestodene 75 µg + EE 20 µg versus gestodene 75 µg + EE 30 µg, Outcome 3 Serum osteocalcin at 12 months.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Paoletti 2000	10	6 (3.8)	10	4.4 (4.1)		100%	1.6[-1.87,5.07]

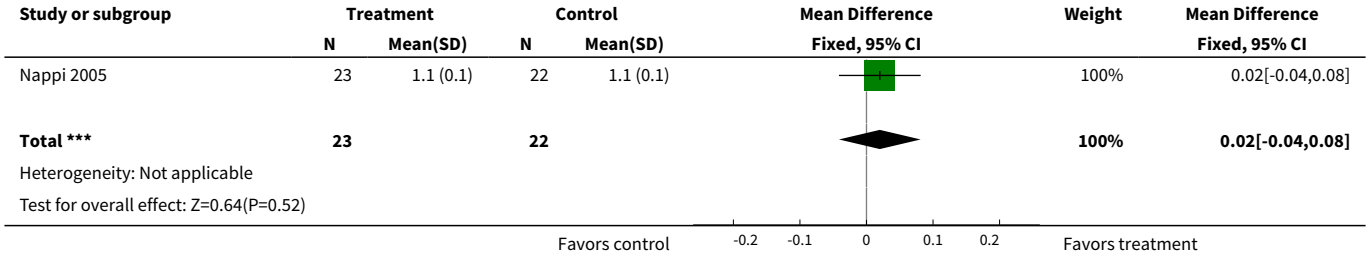




Comparison 13. Drospirenone 3 mg + EE 30 µg versus gestodene 75 µg + EE 30 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density (lumbar spine) at 12 months	1	45	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.04, 0.08]

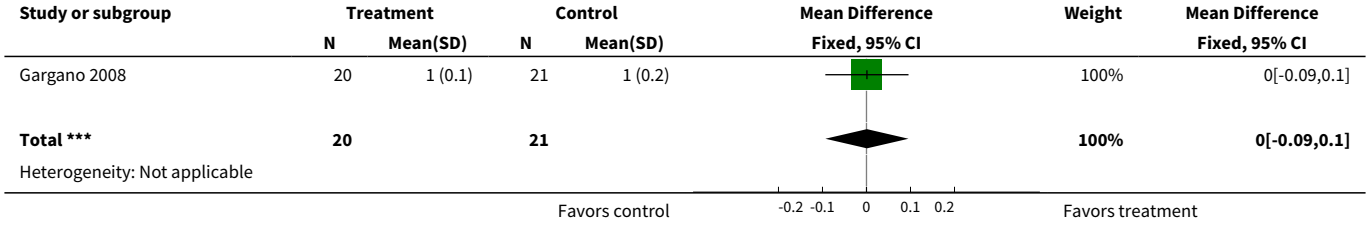
Analysis 13.1. Comparison 13 Drospirenone 3 mg + EE 30 µg versus gestodene 75 µg + EE 30 µg, Outcome 1 Bone mineral density (lumbar spine) at 12 months.

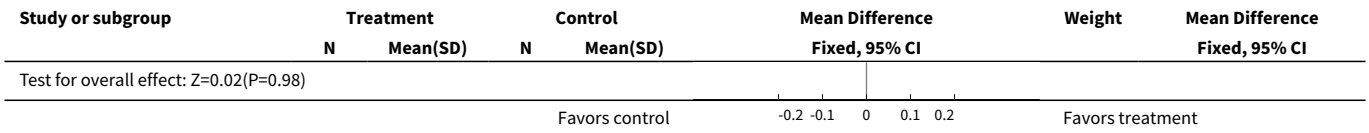


Comparison 14. Drospirenone 3 mg + EE 30 µg versus drospirenone 3 mg + EE 20 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone mineral density (lumbar spine) at 12 months	1	41	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.09, 0.10]

Analysis 14.1. Comparison 14 Drospirenone 3 mg + EE 30 µg versus drospirenone 3 mg + EE 20 µg, Outcome 1 Bone mineral density (lumbar spine) at 12 months.

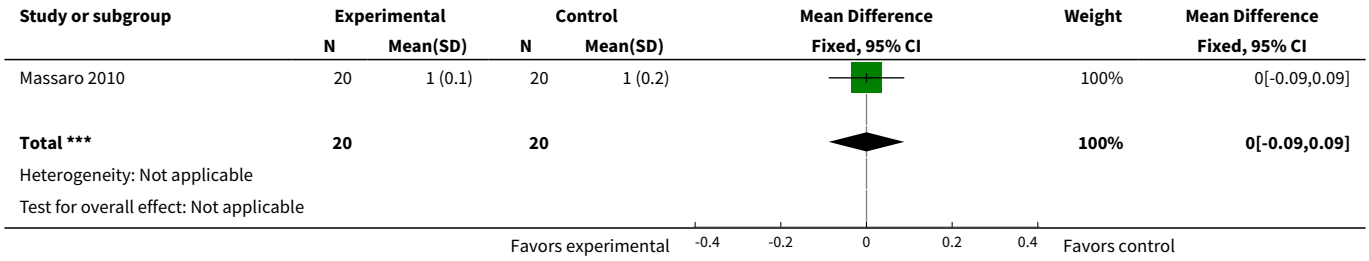




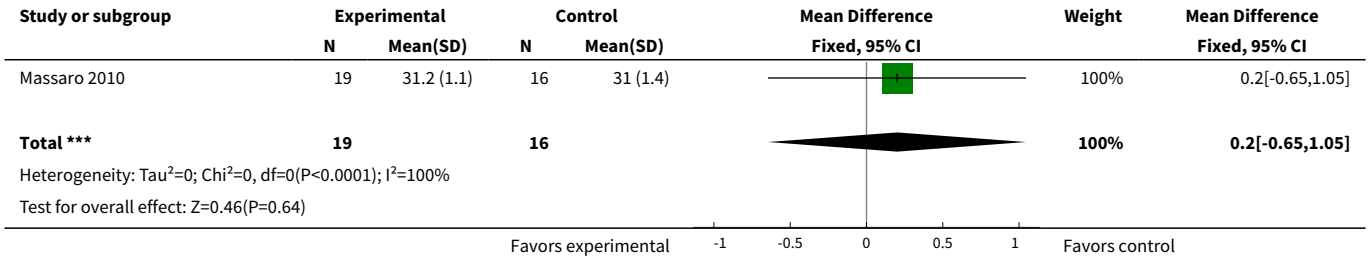
Comparison 15. Transdermal patch (norelgestromin 150 µg plus EE 20 µg) versus vaginal ring (etonogestrel 120 µg plus EE 15 µg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lumbar spine BMD at 12 months	1	40	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.09, 0.09]
2 Urinary pyridinoline at 12 months	1	35	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.65, 1.05]
3 Urinary deoxypyridinoline at 12 months	1	35	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.24, 0.44]
4 Serum osteocalcin at 12 months	1	35	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.26, 0.26]

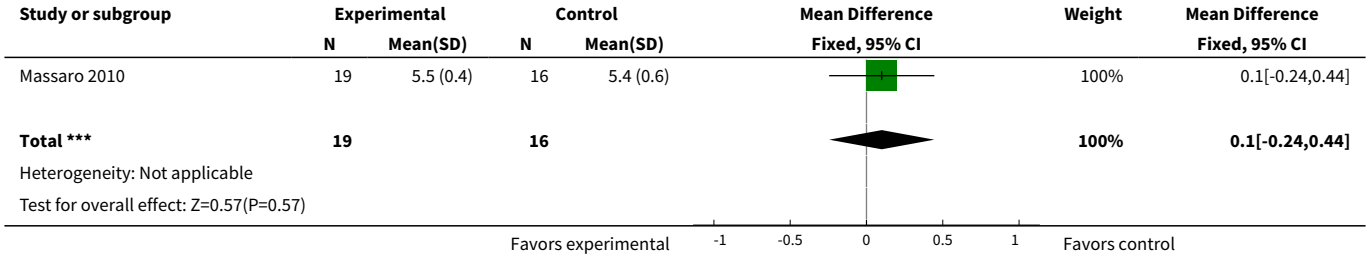
Analysis 15.1. Comparison 15 Transdermal patch (norelgestromin 150 µg plus EE 20 µg) versus vaginal ring (etonogestrel 120 µg plus EE 15 µg), Outcome 1 Lumbar spine BMD at 12 months.



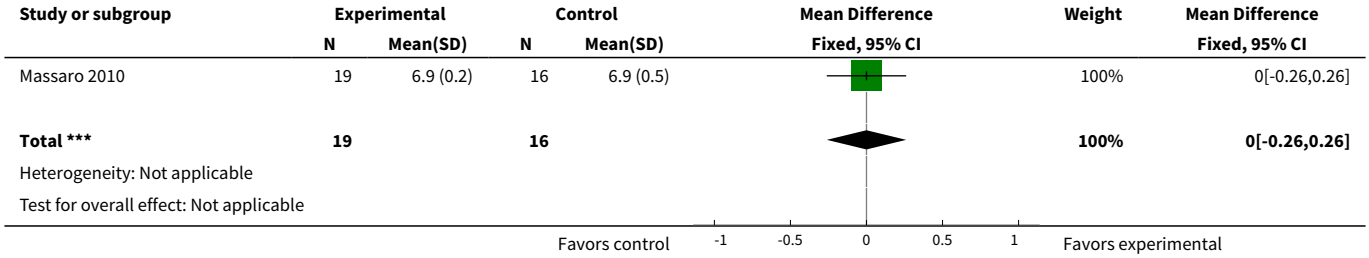
Analysis 15.2. Comparison 15 Transdermal patch (norelgestromin 150 µg plus EE 20 µg) versus vaginal ring (etonogestrel 120 µg plus EE 15 µg), Outcome 2 Urinary pyridinoline at 12 months.



Analysis 15.3. Comparison 15 Transdermal patch (norelgestromin 150 µg plus EE 20 µg) versus vaginal ring (etonogestrel 120 µg plus EE 15 µg), Outcome 3 Urinary deoxypyridinoline at 12 months.



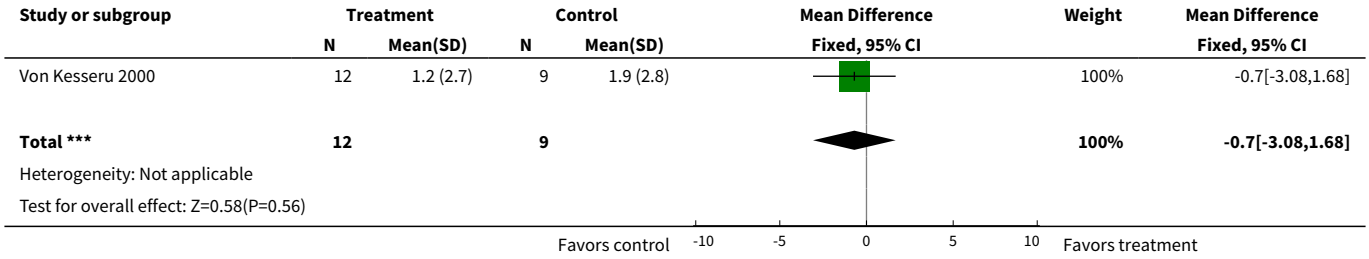
Analysis 15.4. Comparison 15 Transdermal patch (norelgestromin 150 µg plus EE 20 µg) versus vaginal ring (etonogestrel 120 µg plus EE 15 µg), Outcome 4 Serum osteocalcin at 12 months.



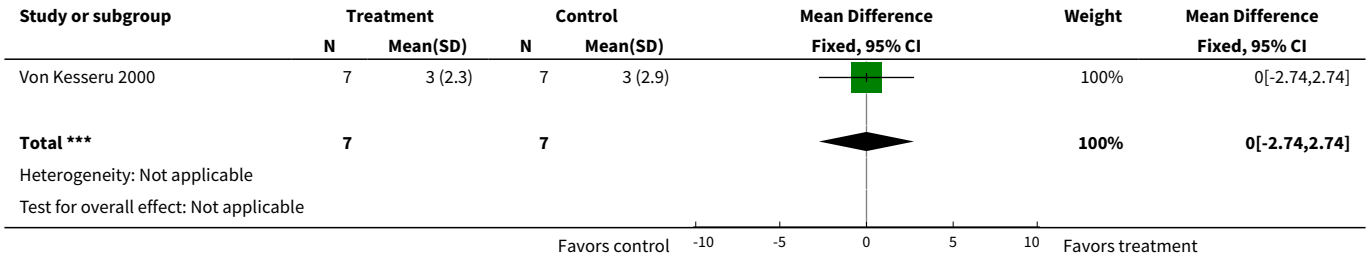
Comparison 16. Norethisterone enanthate 50 mg + estradiol valerate 5 mg versus Nova T IUD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percent change in bone mineral density (lumbar spine) by 12 months	1	21	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-3.08, 1.68]
2 Percent change in bone mineral density (lumbar spine) by 24 months	1	14	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.74, 2.74]

Analysis 16.1. Comparison 16 Norethisterone enanthate 50 mg + estradiol valerate 5 mg versus Nova T IUD, Outcome 1 Percent change in bone mineral density (lumbar spine) by 12 months.



Analysis 16.2. Comparison 16 Norethisterone enanthate 50 mg + estradiol valerate 5 mg versus Nova T IUD, Outcome 2 Percent change in bone mineral density (lumbar spine) by 24 months.



ADDITIONAL TABLES

Table 3. Outcomes by 18 months (Cibula 2012)

Outcome at 18 months (crossover at 9 months)[1]	Variable[2]	Reported F-ratio	Reported P value
Change in lumbar spine BMD (g/cm2)	dose	4.6	0.037
Change in propeptide of type I procollagen (µg/l)	dose	8.3	0.005
Change in cross-linked telopeptide (µg/l)	dose	0.7	0.397

[1]From full ANOVA model for crossover design; reportedly adjusted for intraindividual variability, sequence of treatment, period of trial, initial value of outcome measure, age, and smoking. Report did not mention ANOVA for the other BMD measures.
[2]Gestodene 75 µg plus EE 30 µg versus gestodene 60 µg plus EE 15 µg; participants were switched to the other formulation at 9 months

Table 4. Summary of outcome data

Study	Comparison groups	Bone mineral density: # differences/ # measures[1]	Biochemical markers: # differences/ # measures
Progestin-only contraceptives			
Implants			
Di 1999	levonorgestrel 6-rod (standard) vs levonorgestrel 6-rod (domestic)	1/4	0/4
Bahamondes 2006	etonogestrel 1-rod vs levonorgestrel 2-rod	2/5	---
Injectable DMPA			
Naessen 1995	DMPA vs	insufficient data	1/4

Table 4. Summary of outcome data *(Continued)*

	levonorgestrel 6-rod implant		
Cromer 2005	DMPA + E_2C vs DMPA + placebo	7/8	---
Cundy 2003	DMPA + conjugated estrogens 62.5 µg vs DMPA + placebo	2/10	---
Kaunitz 2009	DMPA subcutaneous vs DMPA intramuscular	1/6	---
Combination contraceptives			
Oral contraceptives			
Berenson 2001	norethindrone 1 mg + EE 35 µg vs desogestrel 150 µg + EE 30 µg	1/2	---
Gai 2012	desogestrel 150 µg + EE 30 µg vs cyproterone acetate 2 mg + EE 35 µg	0/4	---
Endrikat 2004	levonorgestrel 100 µg + EE 20 µg vs levonorgestrel 150 µg + EE 30 µg	0/4	0/2
Hartard 2006	levonorgestrel 100 µg + EE 20 µg vs desogestrel 150 µg + EE 20 µg	0/2	1/3
Rad 2011	levonorgestrel 90 µg + EE 20 µg (continuous) vs levonorgestrel 100 µg + EE 20 µg (cyclic)	---	insufficient data
Sordal 2012	nomegestrol 2.5 mg + 17ß estradiol 1.5 mg vs levonorgestrel 150 µg + EE 30 µg	0/2	---
Paoletti 2000	gestodene 75 µg + EE 20 µg vs gestodene 75 µg + EE 30 µg	---	1/3
Nappi 2003	gestodene 75 µg + EE 20 µg vs gestodene 60 µg + EE 15 µg	insufficient data	insufficient data
Cibula 2012	gestodene 75 µg + EE 30 µg vs gestodene 60 µg + EE 15 µg	1/1	insufficient data
Nappi 2005	drospirenone 3 mg + EE 30 µg vs gestodene 75 µg + EE 30 µg	0/1	insufficient data
Gargano 2008	drospirenone 3 mg + EE 30 vs drospirenone 3 mg + EE 20	0/1	insufficient data

Table 4. Summary of outcome data *(Continued)*

Injectable			
Von Kesseru 2000	norethisterone enanthate + E_2V vs Nova-T IUD	0/2	---
Patch versus ring			
Massaro 2010	transdermal patch vs vaginal ring	0/1	0/3

[1]Number of significant differences between study group divided by number of outcome measures (e.g., lumbar spine, femoral neck).

Table 1. Evidence quality

Study	Comparison groups	Inadequate randomization and allocation concealment	No blinding	Follow up <= 12 months (only BMD)	Losses > 20%	Quality of evidence[1]
Injectable (versus implant, injectable, or IUD)						
Naessen 1995	DMPA vs LNG 6-rod implant	---	unclear	---	---	high
Cromer 2005	DMPA + E_2C vs DMPA + placebo	---	---	---	-1	moderate
Cundy 2003	DMPA + estrogen vs DMPA + placebo	---	---	---	-1	moderate
Kaunitz 2009	DMPA-subcutaneous vs DMPA-intramuscular	---	---	---	-1	moderate
Evidence quality from 4 DMPA trials						*moderate*
Implants						
Di 1999	levonorgestrel 6-rod (standard) vs levonorgestrel 6-rod (domestic)	-1	unclear	---	---	moderate
Bahamondes 2006	etonogestrel 1-rod vs levonorgestrel 2-rod	---	unclear	---	---	high
Evidence quality from 2 implant trials						*moderate to high*

Table 1. Evidence quality *(Continued)*

Combined oral contraceptives						
Berenson 2001	norethindrone 1 mg + EE 35 µg vs desogestrel 150 µg + EE 30 µg	-1	---	-1	-1	very low
Gai 2012	desogestrel 150 µg + EE 30 µg vs cyproterone acetate 2 mg + EE 35 µg	-1	unclear	---	---	moderate
Endrikat 2004	levonorgestrel 100 µg + EE 20 µg vs levonorgestrel 150 µg + EE 30 µg	-1	---	---	-1	low
Hartard 2006	levonorgestrel 100 µg + EE 20 µg vs desogestrel 150 µg + EE 20 µg	-1	-1	---	---	low
Rad 2011	levonorgestrel 90 µg + EE 20 µg (continuous) vs levonorgestrel 100 µg + EE 20 µg (cyclic)	---	-1	---	-1	low
Sordal 2012	nomegestrol 2.5 mg + 17ß estradiol 1.5 mg vs levonorgestrel 150 µg + EE 30 µg	-1	-1	---	-1	very low
Paoletti 2000	gestodene 75 µg + EE 20 µg vs gestodene 75 µg + EE 30 µg	---	-1	---	---	moderate
Nappi 2003	gestodene 75 µg + EE 20 µg vs gestodene 60 µg + EE 15 µg	---	unclear	---	---	high
Cibula 2012	gestodene 75 µg + EE 30 µg vs gestodene 60 µg + EE 15 µg	---	unclear	---	---	high
Nappi 2005	drospirenone 3 mg + EE 30 µg vs gestodene 75 µg + EE 30 µg	---	-1	-1	---	low
Gargano 2008	drospirenone 3 mg + EE 30 vs drospirenone 3 mg + EE 20	-1	unclear	-1	---	low
Evidence quality from 11 COC studies						*low*
Injectable or patch versus ring						
Von Kesseru 2000	norethisterone enanthate + E_2V vs Nova-T IUD	---	---	---	-1	moderate
Massaro 2010	transdermal patch vs vaginal ring	---	---	---	---	high

Table 1. Evidence quality *(Continued)*

Evidence quality from 2 trials of injectable or patch versus ring	*moderate to high*
Overall evidence quality from 19 trials	***moderate***

[1]Grade levels were high, moderate, low, or very low. RCTs were downgraded one level for each of the following: a) randomization sequence generation and allocation concealment: no information on either, or one was inadequate; b) no blinding; c) follow up <= 12 months for BMD only; d) losses >= 20% for primary analysis.

Table 2. Sensitivity analysis

Study[1]	Comparison groups	Fracture	Bone mineral density[2]	Biochemical markers[2]
Injectable DMPA				
Naessen 1995	DMPA vs levonorgestrel 6-rod implant	---	---	1/4
Cromer 2005	DMPA + E_2C vs DMPA + placebo supplement	---	7/8	---
Cundy 2003	DMPA + estrogen vs DMPA + placebo supplement	---	2/10	---
Kaunitz 2009	DMPA subcutaneous vs DMPA intramuscular	---	1/6	---
Implants				
Di 1999	levonorgestrel 6-rod (standard) vs levonorgestrel 6-rod (domestic)	---	1/4	0/4
Bahamondes 2006	etonogestrel 1-rod vs levonorgestrel 2-rod	---	2/5	---
Combined oral contraceptives				
Gai 2012	desogestrel 150 µg + EE 30 µg vs cyproterone acetate 2 mg + EE 35 µg	---	0/4	---
Paoletti 2000	gestodene 75 µg + EE 20 µg vs gestodene 75 µg + EE 30 µg	---	---	1/3
Cibula 2012	gestodene 75 µg + EE 30 µg vs gestodene 60 µg + EE 15 µg	---	1/1	---
Combination injectable or patch versus ring				

Table 2. Sensitivity analysis *(Continued)*

Von Kesseru 2000	norethisterone enanthate + E_2V vs Nova-T IUD	---	0/2	---
Massaro 2010	transdermal patch vs vaginal ring	---	0/1	0/3

[1]Provided sufficient data for that outcome (Table 4) and the evidence was moderate or high quality (Table 1).
[2]From Table 4: number of outcome measures showing a significant difference between study groups divided by number of outcome measures.

APPENDICES

Appendix 1. Search 2014

MEDLINE via PubMed (01 Jan 2011 to 07 May 2014)

(contraceptive agents, female OR ((steroid OR steroids OR steroidal) AND contracept*) OR ortho evra OR "ortho evra" OR "norelgestromin" OR (contraceptive devices, female and ring) OR NuvaRing OR cyclofem OR lunell* OR mesigyna OR cycloprovera OR (medroxyprogesterone 17-acetate AND (contracept* OR inject* OR depo OR depot)) OR depot medroxyprogesterone OR depo medroxyprogesterone OR depot medroxyprogesterone OR depomedroxyprogesterone OR dmpa OR "net en" OR norethisterone enanthate OR norplant OR uniplant OR jadelle OR implanon OR ((levonorgestrel OR etonogestrel) AND implant) OR (levonorgestrel AND intrauterine device*) OR mirena OR ((progestational hormones OR progestin) AND contracept* AND (oral OR pill* OR tablet*))) AND (bone density OR fracture* OR osteoporosis OR "bone mass" OR "bone mineral density" OR "bone density" OR "bone turnover" OR "bone mineral content" OR "bone loss" OR "bone resorption") NOT hormone replacement therapy AND (Clinical Trial[ptyp])

POPLINE (2011 to 25 Nov 2013)

All fields:
bone AND (fracture OR density OR turnover OR mineral OR mass OR loss OR resorption)

Keyword:
contraceptive agents, female
OR contraceptive methods

CENTRAL (01 Jan 2011 to 25 Nov 2013)

contracept* AND (fracture* OR bone) [in Title, Abstract, or Keywords]
NOT exercise OR postmenopaus* OR hypothalamic OR hirsutism [in Record Title]

EMBASE (2011 to 21 Nov 2013)

contraceptive* OR 'contraception'/exp AND ('bone'/exp AND 'density'/exp OR 'fracture'/exp) NOT 'postmenopause'/exp AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [humans]/lim

LILACS (01 Jan 2011 to 16 Dec 2013)

contraceptive agents, female or contraception or contraceptives or contraceptive [Words] and bone or bones or fracture or fractures [Words]

ClinicalTrials.gov (01 Jan 2011 to 15 May 2014)

Study type: Interventional studies
Condition: NOT (polycystic OR cancer OR endometriosis OR menopause)
Intervention: contraceptive OR contraception
Outcome measures: fracture OR bone
Gender: studies with female participants

ICTRP (01 Jan 2011 to 15 May 2014)

Title: fracture OR bone
Intervention: contraception OR contraceptive

Appendix 2. Previous searches

2011 update

MEDLINE via PubMed (Sep 2009 to 08 Jun 2011)

(contraceptive agents, female OR ((steroid OR steroids OR steroidal) AND contracept*) OR ortho evra OR "ortho evra" OR "norelgestromin" OR (contraceptive devices, female and ring) OR NuvaRing OR cyclofem OR lunell* OR mesigyna OR cycloprovera OR (medroxyprogesterone 17-acetate AND (contracept* OR inject* OR depo OR depot)) OR depot medroxyprogesterone OR depo medroxyprogesterone OR depot medroxyprogesterone OR depomedroxyprogesterone OR dmpa OR "net en" OR norethisterone enanthate OR norplant OR uniplant OR jadelle OR implanon OR ((levonorgestrel OR etonogestrel) AND implant) OR (levonorgestrel AND intrauterine devices) OR mirena OR ((progestational hormones OR progestin) AND contracept* AND (oral OR pill* OR tablet*))) AND (bone density OR fracture* OR osteoporosis OR "bone mass" OR "bone mineral density" OR "bone density" OR "bone turnover" OR "bone mineral content" OR "bone loss" OR bone resorption) NOT hormone replacement therapy

POPLINE (2008 to 08 Jun 2011)

(Contraceptive Agents Female/depo provera/dmpa/medroxyprogesterone/(steroid* & contracept*) /orthoevra/ortho evra / norelgestromin/(contraceptive devices, female and ring)/ NuvaRing /cyclofem /lunelle/ mesigyna/ cycloprovera/ (medroxyprogesterone 17-acetate & (contracept* /inject*/depo/depot))/ depot medroxyprogesterone/ depo medroxyprogesterone/ depot medroxyprogesterone/ depo medroxyprogesterone/dmpa/ net en/ norethisterone-enantate/norplant/uniplant/jadelle/implanon/((levonorgestrel/ etonogestrel) & implant)/(levonorgestrel & intrauterine devices)/mirena /((progestational hormones/progestin) & contracept* & (oral/pill*/tablet*)))& (bone/fracture*& bone density/fracture*/osteoporosis/bone mass/ bone mineral density/ bone density/bone turnover/bone mineral content/bone loss/bone resorption) !(hormone replacement therapy/HRT)

CENTRAL (2008 to 08 Jun 2011)

contracept* AND (fracture* OR bone) [in Title, Abstract, or Keywords]
NOT exercise OR postmenopaus* OR hypothalamic OR hirsutism [in Record Title]

LILACS (to 29 Mar 2011)

contraceptive agents, female or contraception or contraceptives or contraceptive [Words] and bone or bones or fracture or fractures [Words]

ClinicalTrials.gov (to 29 Mar 2011)

Condition: NOT (polycystic OR cancer OR endometriosis OR menopause)
Intervention: contraceptive OR contraception
Outcome measures: fracture OR bone
Gender: studies with female participants

ICTRP (to 29 Mar 2011)

Title: fracture OR bone
Intervention: contraception OR contraceptive

Initial review (2006) and 2009 update

The strategies were as listed above for 2011 update. In addition, EMBASE was searched using the strategy shown below.

EMBASE

(contraceptive agent or steroid? (w)contracept?)
AND
bone density or fracture?
NOT
(hormone substitution or estrogen therapy)

WHAT'S NEW

Date	Event	Description
7 May 2014	New search has been performed	Search updated.

Date	Event	Description
25 March 2014	New citation required but conclusions have not changed	Three new trials included (Cibula 2012; Gai 2012; Sordal 2012); one ongoing trial added (Bonny 2013); one study excluded (Berenson 2012).
27 January 2014	Amended	Criteria revised for assessing evidence quality (Data synthesis; Table 1). Sensitivity analysis added (Table 2).

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 4, 2006

Date	Event	Description
8 June 2011	New search has been performed	Searches were updated for MEDLINE, POPLINE, and CENTRAL
21 April 2011	New citation required but conclusions have not changed	Three new trials were included (Kaunitz 2009; Massaro 2010; Rad 2011). Other studies were excluded or added as Ongoing studies.
29 March 2011	New search has been performed	Searches were updated
18 December 2008	New citation required but conclusions have not changed	Added: two new trials (Gargano 2008; Hartard 2006), follow-up data from earlier trial (Bahamondes 2006), and an ongoing trial (Schering-Plough 2011a). An additional trial was excluded (Teichmann 2009a).
24 November 2008	New search has been performed	Searches updated in Nov and Dec 2008
15 April 2008	Amended	Converted to new review format.
28 June 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

LM Lopez conducted the primary data abstraction and developed the review. Through the 2011 update, DA Grimes did the secondary data abstraction and KF Schulz provided statistical oversight. K Curtis contributed to the search methods. For the 2014 update, M Chen reviewed the evidence quality assessment and advised on presentation of statistics. All authors edited the manuscript and helped interpret the results.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

DECLARATIONS OF INTEREST

DA Grimes has consulted with the pharmaceutical companies Bayer Healthcare Pharmaceuticals and Merck & Co, Inc.

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INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density [*drug effects]; Bone Remodeling [drug effects]; Contraceptives, Oral, Hormonal [adverse effects] [*pharmacology]; Estrogens [pharmacology]; Fractures, Bone [*chemically induced]; Medroxyprogesterone Acetate [adverse effects] [pharmacology]; Premenopause; Progestins [pharmacology]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans