Table S1. Overview of the 9 randomised controlled trials (RCTs), including results of oestrogen hormone therapy (oral contraceptives (OCP), conjugated oestrogens (CE) and transdermal estradiol (TE) on bone mineral density (BMD).

Results of oral contraceptives on bone mineral density					
Country	**Study population**	**Methods**	**Intervention**	**Diagnostic test used**	**Results**
USA, 1997[33]	24 women Aged 14-28 years (mean 19.5 ± 2.2) Hypothalamic amenorrheic women (no menstruation for 6-months) and oligomenorrheic women (≤6 menstrual periods in the past 12-months) due to excessive training, weight loss, dieting or stress Mean lumbar spine BMD (g/cm^2) was 0.90 ± 0.01	RCT of 12-months duration Individual comparison for the amenorrheic and the oligomenorrheic subjects at baseline, 6-months, and 12-months follow-up	*Amenorrheic subjects* Group 1 received OCP (35mcg EE and 0.5-1mg norethindrone) daily on 21 of each 28-day cycle (n=5, age 18.6 ± 3.0) Group 2 received medroxyprogesterone (10mg) daily on the last 12-days of the calendar month (n=5, age 20.3 ± 4.4) Group 3 received placebo daily on the last 12-days of the calendar month (n=5, age 21.3 ± 5.2) *Oligomenorrheic subjects* Group 4 received medroxyprogesterone (10mg) daily on the last 12-days of the calendar month (n=5, age 19 ± 3.6) Group 5 received placebo daily on the last 12-days of the calendar month (n=4, age 17.2 ± 2.0) Drop outs (n=0)	BMD was assessed at lumbar spine, total body and neck of femur using DXA scan	At 12-months, group 1 had a significant increase in lumbar BMD compared to group 2 and 3 (p=0.003 and p=0.009, respectively) At 6- and 12-months group 1 improved mean lumbar BMD by 3.7% and 5.4%, respectively, while group 2 had a mean reduction of 0.6% and 10.2%, respectively; and group 3 a similar mean reduction of 1.4% and 0.8%, respectively Results for the oligomenorrheic group are not applicable as they did not receive target intervention
Spain, 2001[38]	64 women Aged 19-35 years (mean 24.4 ± 1.0) Hypothalamic amenorrheic women (no menstruation for	RCT of 12 months duration Comparison at baseline and 12-months follow-up	Group 1 received OCP (0.030mg EE and 0.15mg desogestrel) (n= 24, age 24.2 ± 5.2) Group 2 received OCP (0.020mg EE and 0.15mg desogestrel) (n= 22, age 25.5 ± 4.4)	BMD was assessed at the lumbar spine using DXA scan	At 12-months group 1 and 2 had a significant mean improvement in lumbar BMD compared to group 3 (both p=<0.05)

	6-months) and oligomenorrheic women (≤6 menstrual periods in the past 12-months), due to stress by depression and anxiety Mean lumbar spine BMD (g/cm^2) was 1.02 ± 0.002		Group 3, the control group, received no intervention (n=18, age 23.4 ± 4.0 Drop outs (n=4), i.e., two in group 1, one in group 2 and one in group 3		No significant between-group change was found for group 1 and 2 At 12-months, group 1 and 2 increased mean lumbar BMD of 2.4% and 2.5%, respectively, while group 3 had a mean 1.1% decrease in lumbar BMD
USA, 2002[35]	60 women Aged 18-38 years (mean 25.2 ± 0.7) Anorexia nervosa classified by DSM-IV criteria and amenorrhea for ≥3 months Mean lumbar spine BMD (g/cm^2) was 0.82 ± 0.002	RCT of 9 months duration Comparison at baseline and 9-month follow-up	All groups received daily calcium 1500mg and a standard multivitamin containing 400IU of vitamin D Group 1 received rhIGF-1 (30mcg/kg sc) twice daily and daily OCP (35mcg EE and 0.4mg norethindrone) (n=16, age 24.2 ± 1.6) Group 2 received rhIGF-1 (30mcg/kg sc) twice daily (n=14, age 23.0 ±1.1) Group 3 received OCP (35mcg EE and 0.4mg norethindrone) and rhIGF-1 placebo (n=15, age 27.6 ± 1.6) Group 4 received rhIGF-1 placebo (n=15 age 26.3 ± 1.5) Drop outs (n=7), i.e., two in group 1, one in group 2 and one in group 4 at baseline; and three in group 2 at 9 months follow-up	BMD was assessed at lumbar spine, total body, distal radius, total hip and femoral neck using DXA scan	At 9-months the 2 x 2 factorial analysis found that mean lumbar BMD increased significantly in group 1 and 2 as compared to group 3 and 4 combined (p=0.05) No significant change was found between group 1 and 3 vs. group 2 and 4 combined (p=0.021) Group 1 and 2 had increased mean lumbar BMD of 1.8% and 0.4%, respectively, while group 3 and 4 reduced their mean BMD by -0.4% and -1.1%, respectively Only group 1 showed within-group statistically significant improvement (p<0.05)
USA, 2006[36]	112 women Aged 11-17 years (mean 15.2 ± 0.1)	RCT of 13 28-day cycles duration	Both groups received multivitamin containing 400 IU Vitamin D and 500mg calcium carbonate daily	BMD at lumbar spine and hip by DXA scan	After cycle 6, group 1 had statistically significant increase in lumbar spine BMD compared to group 2 (p=0.021) but not after cycle 13 (p=0.244)

	Premenopausal girls with anorexia nervosa, classified by DSM-IV criteria Mean lumbar spine BMD (g/cm^2) was 0.90 ± 0.01	Comparison at baseline and 6- and 13 cycles	Group 1 received OCP (35mcg of EE and 180–250mcg NGM), i.e., active tablets on days 1-21 and inactive tablets on days 22-28. (n=53, age 15.2 ± 1.19) Group 2 received matching placebo (n=59; age 15.1 ± 1.46) Drop outs (n=23), i.e., 13 in group 1 and 10 in group 2		At cycle 6, group 1 and 2 improved their mean lumbar spine BMD by 2.4% and 1%, respectively, which further increased at cycle 13 to 3.1% and 2.4%, respectively
USA, 2007[37]	150 women Aged 18-26 years (mean 22.1 ± 0.3) Competitive female runners from intercollegiate cross-country teams, post-collegiate running clubs, and road races with at least 40 miles per week during peak training times amenorrheic (n=13), oligomenorrheic (n=37), eumenorrheic (n=150) Mean lumbar spine BMD (g/cm^2) was 0.98 ± 0.004	RCT of 24 months duration Comparison at baseline and 12- and 24-months follow-up	Group 1 received OCP (30mcg of EE and 0.3mg of norgestrel), 28-day pack (n=69; age 22.3 ± 2.7) Group 2, the control group, did not receive any intervention (n=81; age 21.9 ± 2.6) Drop outs (n=26, i.e., 15 in group 1 and 11 in group 2	BMD and BMC were measured at proximal femur, lumbar spine and whole body by DXA scan	No significant between-group change was seen at both follow-up time points The annual rate of change in lumbar spine BMD increased by 0.8% and 0.7% in group 1 and group 2, respectively
Results of conjugated oestrogens on bone mineral density					
GB, 1999[34]	34 women Aged 18-35 years (mean 27.4 ± 2.4) Long-distance amenorrheic (n=25) and oligomenorrheic (n=9) runners running ≥	RCT of 18 months duration Comparison at baseline and 9- and 18-months follow-up	Group 1 received CE (1mg estriol and 2mg estradiol for 12-days; 1mg estriol, 2mg estradiol and 1mg norethisterone acetate for 10-days; 0.5mg estriol and 1mg estradiol for 6-days), plus 1000mg calcium carbonate (n=10, age 28.4 ± 4.8)	BMD was assessed at lumbar spine, neck of femur, trochanteric region, and ward's triangle using DXA scan	No statistically significant between-groups differences in lumbar BMD were found at 9-months, while group 1 showed a within-group significant increased BMD at 9-months ($p<0.05$)

	40km/week and ≥ 3h/week, having: Mean lumbar spine BMD (g/cm^2) was 0.95 ± 0.02		Group 2 received 1000mg calcium carbonate (n=14, age 28.7 ± 6.0) Group 3, the control group, received no intervention (n=10, age 25 ± 5.3) Drop outs (n=3), i.e., one in group 1 and two in group 2		At 9-months, the lumbar BMD increased by 5.7% in group 1, while it decreased by 0.03% and 0.3% in group 2 and 3, respectively Due to high drop outs (>50%), follow-up data for 18-months were not presented
USA, 2003[39]	55 women Aged 17-26 years (mean 21.6 ± 2.4) Exercising elite ballet dancers with mean number of hours/week spent dancing 24 ± 10.8, amenorrheic (n=24), eumenorrheic (n=31) Mean lumbar spine BMD (g/cm^2) was 1.22 g/cm^2 ± 0.06	RCT of 24 months duration Comparison at baseline and 24-months follow-up	All groups received 1250mg of calcium per day. Group 1 (amenorrheic) received CE (Premarin 0.625mg on days 1 to 25; and Medroxyprogesterone acetate, 10mg, on days 16 to 25, in a 30-day cycle. (n=13, age 20.8 ± 3.1) Group 2 (amenorrheic) received placebo (n=11, age 19.2 ± 3.4) Group 3 (eumenorrheic) control group, received no intervention (n=31, age 24 ± 4.6) Drop outs (n=29), i.e., 11 in group 1 and 2 combined and 18 in group 3	BMD was assessed at the lumbar spine, foot and wrist using dual photon absorptiometry (DPA)	No significant within- or between- group change were seen for lumbar BMD at follow-up time points for and between group 1 and 2 The lumbar BMD improved by 5.6%, 4.5% and 6.7% at 24-months follow-up in group 1, 2 and 3 respectively
Results of transdermal estradiol on bone mineral density					
USA, 2011[20]	150 women Aged 12-18 years (mean 16 ± 0.2) Anorexia nervosa classified by DSM-IV criteria and amenorrhea for ≥3-months	RCT of 18 months duration Comparison at baseline and 6-, 12- and 18-months follow-up	All groups received 1200mg calcium and 400IU vitamin D daily Subjects who received active intervention (group 1) received individualized treatment according to their bone age (BA), i.e., mature (BA	BMD was assessed at the lumbar spine and hip using DXA scan	Mature and immature subjects were analysed combined in group 1 and 2, respectively Group 1 had significant increased lumbar BMD as compared to group 2 at 6-, 12- and 18-months follow-up

	Mean lumbar spine BMD (g/cm^2) was 0.94 ± 0.03		≥15 years, n=96) or immature (BA<15 years, n=14) Group 1, *Mature AN,* received transdermal 17-β estradiol patch (with cyclic progesterone) (100mcg twice/weekly); and medroxyprogesterone (2.5mg) daily for 10-days each month *Immature AN* (BA<15 years, n=14) received escalating doses of oral EE (3.75mcg, 7.5mcg, followed by 11.25mcg daily, dose adjusted every six months for 18-months (n=55, age ?) Group 2, *Mature AN,* received placebo patch and placebo medroxyprogesterone daily for 10-days each month *Immature AN* received oral placebo (n=55, age ?) Group 3, normal weight controls, did not receive any intervention (n=40, age 15.6±0.2) Drop outs (n=60), at baseline (n=4), i.e., three in group 1 and one in group 2; at 6-months (n=22), i.e., 12 in group 1, eight in group 2 and two in group 3; at 12-months (n=17), i.e., six in group 1, seven in group 2 and four in group 3; at 18-months follow-up (n=17), i.e., three in group 1, nine in group 2 and five in group 3		regardless of confounders adjusted for, i.e., age, weight changes, height, years since menarche and/or duration of amenorrhea (all adjusted p-values <0.02) At 6-, 12-, and 18-months, group 1 and 3 improved the mean lumbar BMD by 1.8%, 2.5%, 2.6%, and 2.3%, 3.3%, 4.5%, respectively; Group 2 had a mean reduced lumbar BMD by -0.5, -0.1 at 6- and 12-months, respectively, which increased by 0.3% at 18-months follow-up

USA, 2019[21]	121 women Aged 14–25 years (mean 19.8 ± 0.5) Oligo-amenorrhoeic endurance athletes, that is, ≥4 hours of aerobic weight-bearing training and/or ≥20 miles of running weekly, and no menstruation for ≥3 months within a ≥6-month period, or absence of menarche at ≥15 years Mean lumbar spine BMD (g/cm^2) was 0.93 ± 0.02	RCT of 12 months duration Comparison at baseline and 6- and 12-months follow-up	All groups received ≥1200mg elemental calcium and 800IU vitamin D daily Group 1 received transdermal 17-β estradiol patch (100mcg twice/weekly) and cyclic micronised progesterone (200mg) for 12 days each month. (n=43; age 19.9±0.4) Group 2 received OCP (30mcg EE with 0.15mg desogestrel) (n=40; age 20.3±0.4) Group 3, the control group, did not receive any intervention (n=38; age 19.4±0.4) Drop outs (n=48), at baseline (n=2), i.e., two in group 1; at 6-months (n=34), i.e., 14 in group 1, 12 in group 2 and eight in group 3; at 12-months follow-up (n=12), i.e., two in group 1, six in group 2 and four in group 3	BMD was assessed at the lumbar spine, femoral neck, total hip and total body less head using DXA scan	At 6-months, group 1 showed significantly increased lumbar BMD as compared to group 2 and group 3 (p=0.014 and p=0.060, respectively), which sustained significant at 12-months follow-up, (p=0.015 and p=0.003, respectively) No significant difference was found between group 2 and group 3 at 6- and 12-months follow-up (p=0.489 and p=0.657, respectively) At 6-months follow-up, group 1, 2 and 3 improved their mean lumbar BMD by 2.7%, 0.8%, and 1.3 % respectively At 12-months, group 1 sustained the improvement by 2.4%, and group 2 improved BMD by 0.1% and group 3 reduced their mean BMD by -0.3%

BA, bone age; AN, anorexia nervosa; BMI, body mass index; IU, International Unit; EE, ethinyl estradiol; DXA, dual-energy x-ray absorptiometry; DPA, dual photon absorptiometry; BMC, bone mineral content; NGM, norgestimate; rhIGF-1, recombinant human insulin-like growth factor 1; DHEA, Dehydroepiandrosterone; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition

Figure S1. Flow diagram of study selection.

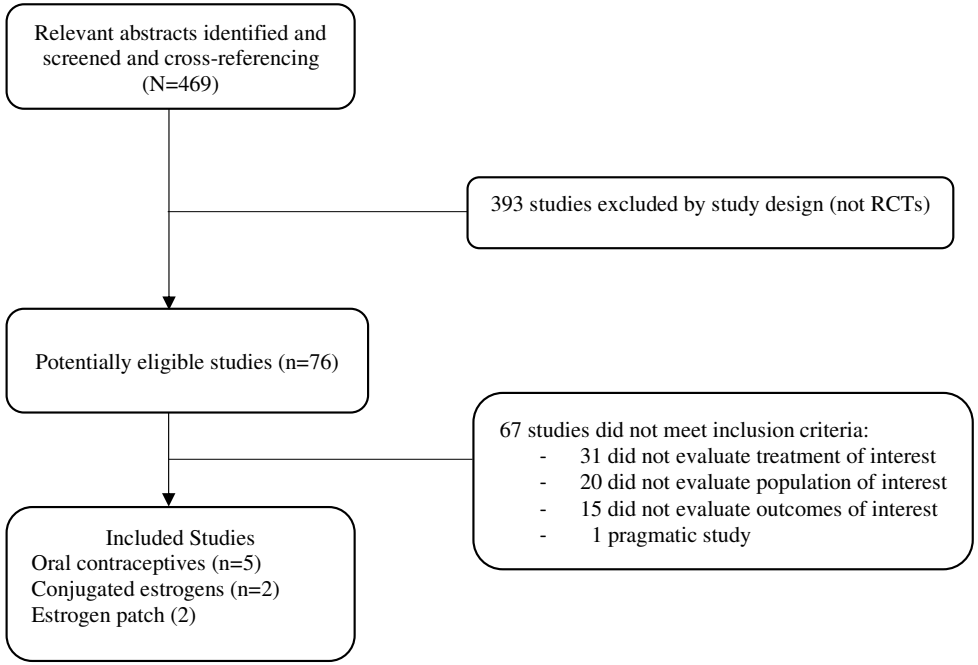

Figure S2. Between group differences in BMD at first assessment point after the intervention (n=167).

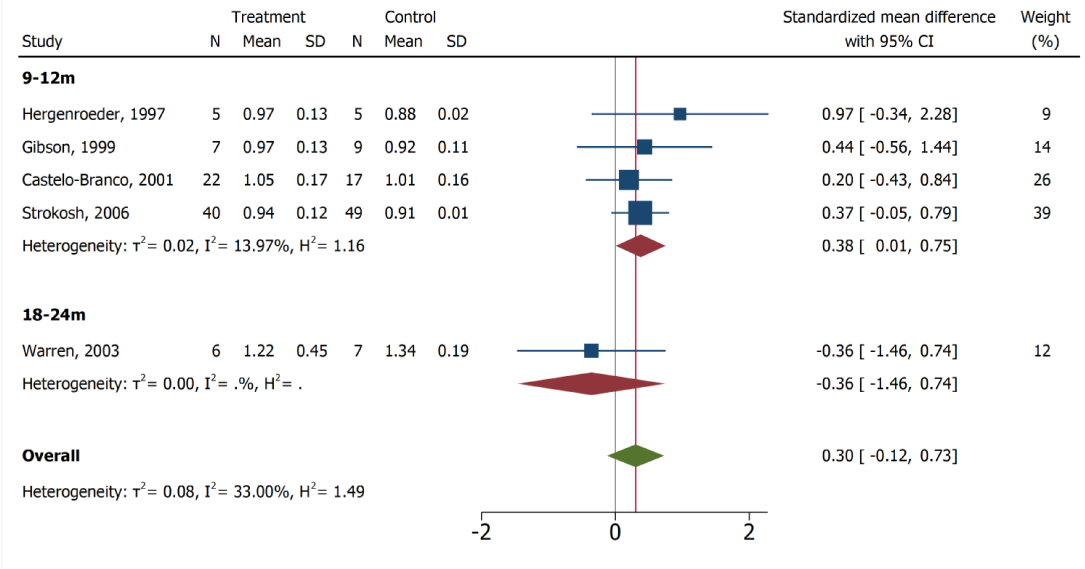

Figure S3. Between group differences in BMD at first assessment point after the intervention with subgroups according diagnostic classification (n=167).

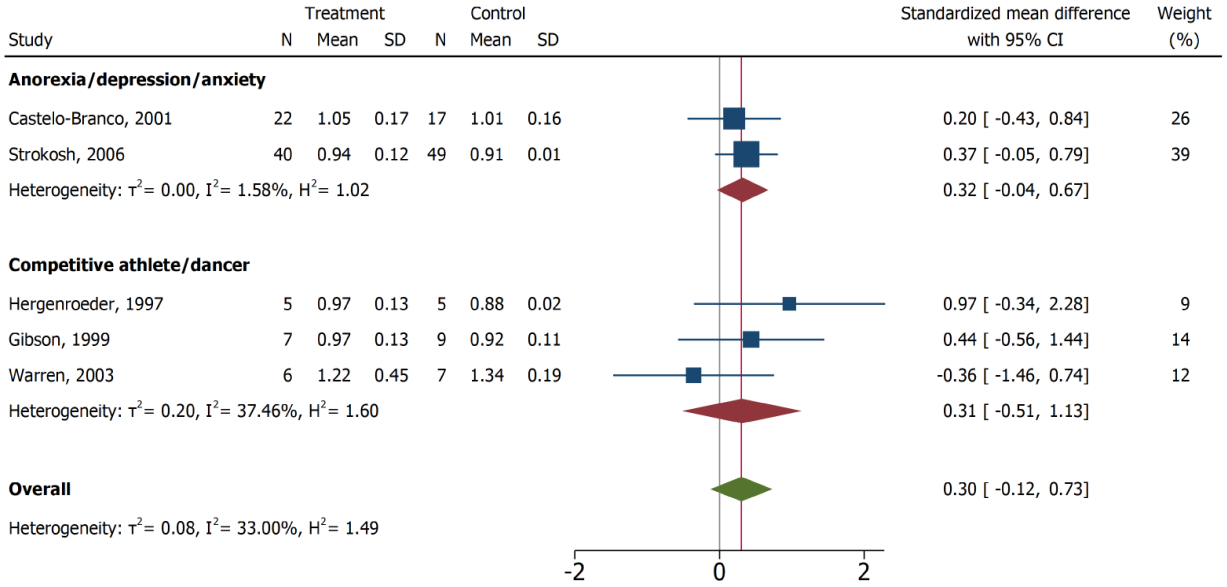

Figure S4. Between group change scores from baseline to first assessment point after the intervention (n=191).

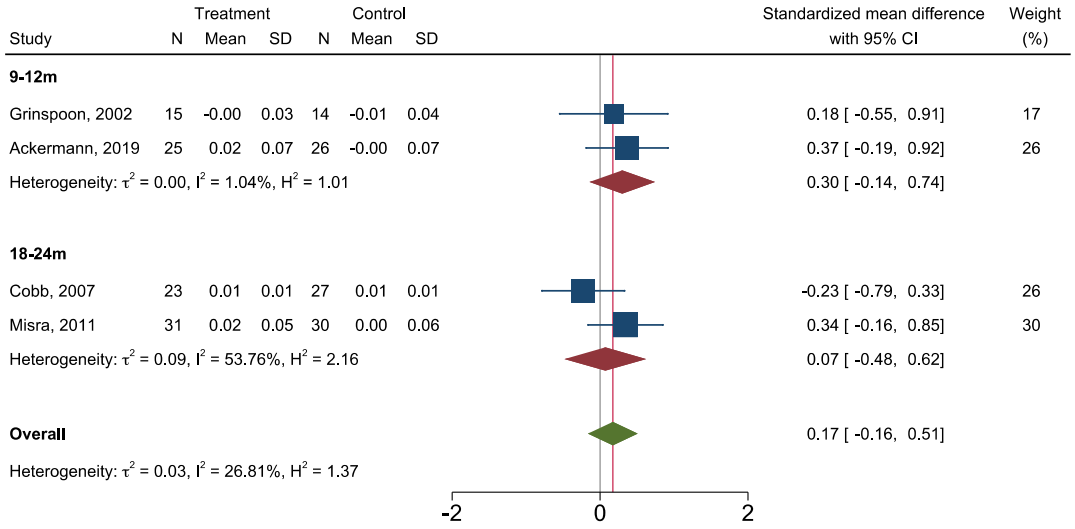

Figure S5. Funnel plot of included randomised controlled trials.

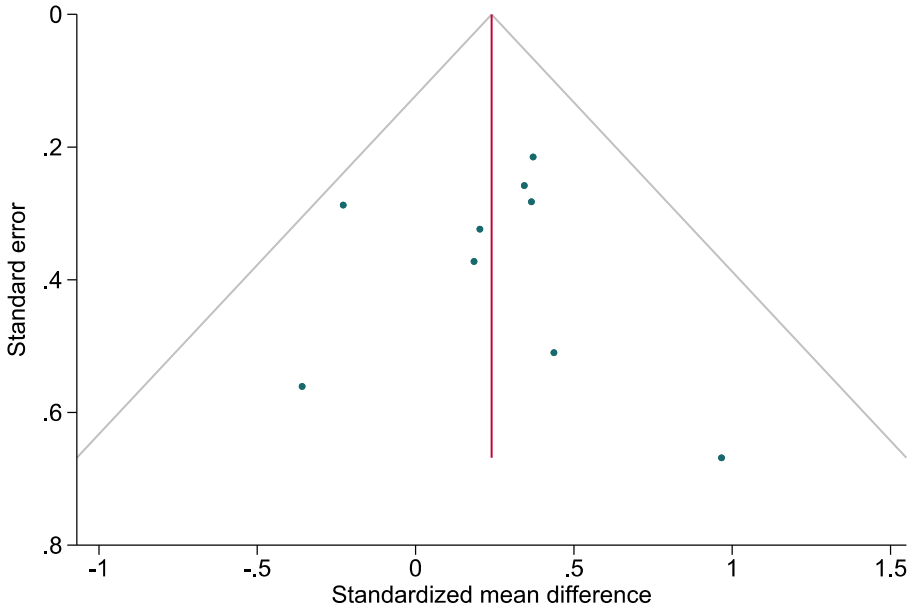

Figure S6. Between group change scores from baseline to first assessment point after the intervention with subgroups according intervention type (pill vs. patch) (n=191).