Supplemental Digital Content 1

Table S1. Search strategy

Table S2. Other characteristics of included trials.

Figure S1. Risk of bias assessment of each eligible study

Figure S2. Funnel plot to assess the presence of publication bias among RCTs included in the review. Individual studies were represented by black dots. The solid line represents the pooled estimate of the effect on the outcome. The dashed lines represent the 95% confidence interval of the effect estimate.

Figure S3. Withdrawals due to adverse effects. (A) cBHT vs. placebo. (B) cBHT vs. therapies using FDA-approved products

Figure S4. Change of serum estrone, estradiol, total testosterone, and free testosterone following compounded DHEA therapy.

Figure S5. Random-effects meta-analysis of (A) the association between cBHT and the change of BMD; (B) the association between compounded oral DHEA and the change of BMD after 1-year therapy.

Figure S6. Random-effects meta-analysis of the association between cBHT and the change of bone markers: (A) BSAP; (B) osteocalcin.

Table S1. Search strategy.

Database	Search terms
PubMed https://pubmed.ncbi.nlm.nih.gov/advanced/	(Estriol OR estradiol OR progesterone OR testosterone OR DHEA) AND (menopause OR postmenopause OR climacteric OR perimenopause) Filter: clinical trial
CENTRAL https://www.cochranelibrary.com/advanced-search	Estradiol OR estriol OR progesterone OR testosterone OR DHEA in Title Abstract Keyword AND menopause OR perimenopause OR postmenopause OR climacteric in Title Abstract Keyword - (Word variations have been searched)
Clinical Trial.gov	Multiple searches will be conducted: 1. Estriol | Studies with Female Participants 2. Menopause | estradiol | Studies with Female Participants 3. Menopause | Testosterone | Studies with Female Participants 4. Menopause | Progesterone | Studies with Female Participants 5. Menopause | DHEA | Studies with Female Participants

Table S2. Other characteristics of included trials.

Study	Participants	Compounding preparation	Power analysis
Barton et al. 2007	Postmenopausal women with a history of cancer and current symptoms of decreased sexual desire. Mean age 52.3 ± 7.89 yr.	Testosterone was prepared in Vanicream	Power 80% - well powered for sexual desire
Davis et al. 2018	Postmenopausal women with invasive breast cancer taking an AI, and with symptoms of vulvovaginal atrophy. No vaginal HRT in the post month or systemic HRT in the preceding 6 months. Mean age 56.4 yr.	Testosterone 300ug/ml in VersaBase® cream was prepared and dispensed by the Health Smart Pharmacy, Alfred Hospital, Melbourne, Australia.	Power 90% - well powered for FSFI satisfaction
Raghunandan et al. 2010	Postmenopausal women with symptoms of urogenital and sexual dysfunction. Age 40-65 yr (mean age 51.7 yr)	Testosterone cream was prepared in petroleum.	Power 81.7% - well powered for sexuality
Fernandes et al. 2014; Fernandes et al. 2016; Fernandes et al. 2018	Postmenopausal women with symptoms of vaginal atrophy. No HRT in the past 6 months. Age 40 to 70 yr (mean age 56.8 yr)	Testosterone cream was prepared using testosterone micronized powder in an emollient cream with silicone to keep the cream iso-osmolar.	Power 80% - well powered for improved dyspareunia, VMV and vaginal pH
Melisko et al. 2017	Postmenopausal women with HR-positive stage I to III breast cancer taking Ais, with vaginal dryness, dyspareunia or decreased libido. No vaginal HRT within the past 30 days. Age 37 to 78 yr (mean 56.5 yr).	Intravaginal testosterone cream was prepared by the UCSF Drug Product Services Laboratory as follows: micronized, USP-grade testosterone powder was levigated with USP-grade mineral oil to form a paste, mixed with a water-miscible odorless compounding vehicle (Velvachol) to produce a 1% concentration	Power 98% - well powered for safety
Gerhard et al. 1998; Seely et al. 1999	Postmenopausal women with mild hypercholesterolemia. Age 48 to 75 yr (mean age 60 yr)	Micronized progesterone (Upjohn) was in a nonliquefying base (Unibase, Warner Chilcott Laboratories)	Not reported
Andreen et al. 2003; Andreen et al. 2004	Postmenopausal women with climacteric symptoms. No HRT 3 months prior to inclusion. Mean age 52 (44-60) yr.	The vaginal formulation was a waxy suppository containing progesterone in a base of semi-synthetic glycerides produced from hydrogenated vegetable oil by interesterification. The vaginal suppositories were prepared by Apoteket AB, Production and Laboratories (the national pharmacy company).	Not reported
Leonetti et al. 1999	Healthy women within 5 years of menopause. Mean age 52.5 yr.	The progesterone was compounded with mixed tocopherol cream to contain 20mg of progesterone per quarter teaspoon.	Powered 80% - well powered for BMD
Lewis et al. 2002	Healthy postmenopausal women aged 43-66. No HRT within the previous 3 months.	Progesterone creams were compounded by Pharmaceutical Compounding NZ Ltd., Auckland, NZ	Not reported
Antoniou et al. 1997	Postmenopausal women with symptoms and signs of atrophic vaginitis due to estrogen deficiency. No estrogens during the past 3 months. Age was 48 to 76 yr (mean age 59.5).	Progesterone in polyethylene glycol was produced as a vaginal suppository.	Not reported
Stephenson et al. 2008	Healthy postmenopausal women aged 43 to 74 yr (median age 57). No HRT in the past 4 weeks.	Transdermal progesterone cream was prepared by the compounding pharmacist using HRT Base, a lipophilic emulsion-type base manufactured by PCCA (Houston, Texas)	Not reported
Wihlback et al. 2005	Healthy postmenopausal women with climacteric symptoms. No HRT within the previous 3 months. Age 52.4 ± 0.8 yr.	Progesterone suppositories were prepared by Apoteket Production and Laboratories.	Not reported
Sood et al. 2013	Postmenopausal women aged 40-60 yr. No vaginal HRT within a week, no transdermal HRT within 4 weeks and no oral HRT within 8 weeks	Bi-est was compounded in Vanicream and dispensed in premarked individual syrings by an experienced compounding pharmacist	Not reported
Thomas et al. 2014	Healthy perimenopausal women aged 52.3 ± 2.2 yr (range 48 to 55). No prior HRT.	Hormone and placebo pills were produced by the Pharmacy Division of Lyon 1 University (Bron)	Not reported
Tanmahasamut et al. 2020	Postmenopausal women aged 45 and older with vaginal symptoms. No previous HRT within 90 days. Mean age 55.7 yr.	Estradiol (Estrofem®) 25 μg in K-Y® Jelly 2 mL was prepared by dissolving a 1 mg estradiol tablet in 5 mL of sterile water for injection. That solution was then added to 75 mL of K-Y® Jelly and mixed well.	Power 80% - well power for VMV
NCT00816556	Postmenopausal women with dryness, itching or burning in and around the vagina. No HRT in the past 3 months.	Estriol 10 μg was added to Vanicream Lite 0.5g. Estradiol cream were prepared by adding estradiol valerate 10 μg to Vanicream Lite 0.5g.	Not reported
Stanczyk et al. 2009	Healthy postmenopausal women aged 55 to 65 yr. No HRT for the past 3 months.	The DHEA tablets were obtained from Belmar Pharmacy (Lakewood, CO)	Underpowered

Bloch et al. 2013	Postmenopausal women aged 45-60 (mean 54.8 yr) who met DSM-IV HSDD criteria.	DHEA was from Fagron, Waregem, Belgium.	Power 80% - underpowered for sexual function
Von Muhlen et al. 2007; Von Muhlen et al. 2008; Kritz-Silverstein et al. 2008	Healthy postmenopausal women. Not using DHEA in the past 6 months. Mean age 68.7 yr (range 55 to 85)	The DHEA supplement for this study was provided by Diosynth, Inc. (Chicago, IL). The DHEA powder was combined with lactose powder, USP (Spectrum Chemical) and packaged in No. 3 empty gelatin capsules (Eli Lilly, Co.).	Power >94% - well powered for BMD
Kenny et al. 2010	Postmenopausal women aged 65 and older and DHEA levels lower than 550ng/dL, low bone mass and frailty. Mean age 76.6 ± 6.0.	DHEA was supplied by Belmar Pharmacy, Lakewood, CO	Underpowered
Casson et al. 1998	Healthy postmenopausal women with low serum DHEAS levels.	The micronized DHEA tablets were provided by Charles Hakala of Belmar Pharmacy (Lakewood, CO)	Underpowered
Stangl et al. 2011	Postmenopausal women aged 55-80 yr, not using HRT	DHEA was compounded by Belmar Pharmaceutical (Lakewood, CO)	Not reported
Casson et al. 1993; Casson et al. 1995	Postmenopausal women aged 45-66 (mean 56.1 yr) with low serum DHEAS levels. No estrogen therapy in the past 3 weeks.	Micronized DHEA was prepared in a wax-vegetable oil matrix with a silica-based excipient. They were supplied by Belmar Pharmaceuticals.	Not reported
Finckh et al. 2005	Postmenopausal women with confirmed fibromyalgia. Mean age 59 yr.	The DHEA preparation was obtained through Hawkins Inc. Pharmaceutical Group, Minneapolis, MN, USA. Study capsules of DHEA 50 mg and identical opaque placebo capsules containing mannitol were produced and packed by the hospital's pharmacy.	Power 80% - well powered for quality of life
Mortola et al. 1990	Postmenopausal women aged 46 to 61 yr and were 30-50% over ideal body weight. No HRT in the previous year.	DHEA was purchased from Sigma Chemical Co. (St. Louis, MO) and packaged in gelatin capsules	Not reported
Gomez-Santos et al. 2011a; Gomez-Santos et al. 2011b	Obese postmenopausal women aged 51 ± 2 yr.	DHEA capsules were made with 100mg of DHEAS and cellulosum microcrystallinum as a filling agent.	Not reported
Jankowski et al. 2006	Healthy postmenopausal women with low serum DHEAS levels. Age 60-88 yr.	Identical DHEA and placebo pills were compounded by the Belmar Pharmacy (Lakewood, CO).	Well powered for BMD
Panjari et al. 2009a; Panjari et al. 2009b	Healthy, sexually active postmenopausal women aged 40 to 65 yr. No HRT in the past 2 months. Mean age 54.5 yr.	DHEA capsules were provided by Endorecherche Inc, Quebec, Canada.	Power 90% - well powered for sexual function
Barton et al. 2018a; Barton et al. 2018b; NCT01376349	Postmenopausal women with a history of cancer and current symptoms of vaginal atrophy. No HRT in the preceding 4 weeks. Mean age 57 yr.	Vaginal DHEA was developed by a compounding pharmacist located in North Dakota. The base included carbomer, squalene, vitamin E acetate USP liquid, distilled water, methylparaben NF powder, propylparaben NF powder, glycerin, and zinc acetate.	Power 80% - well powered for vaginal symptoms

Figure S1

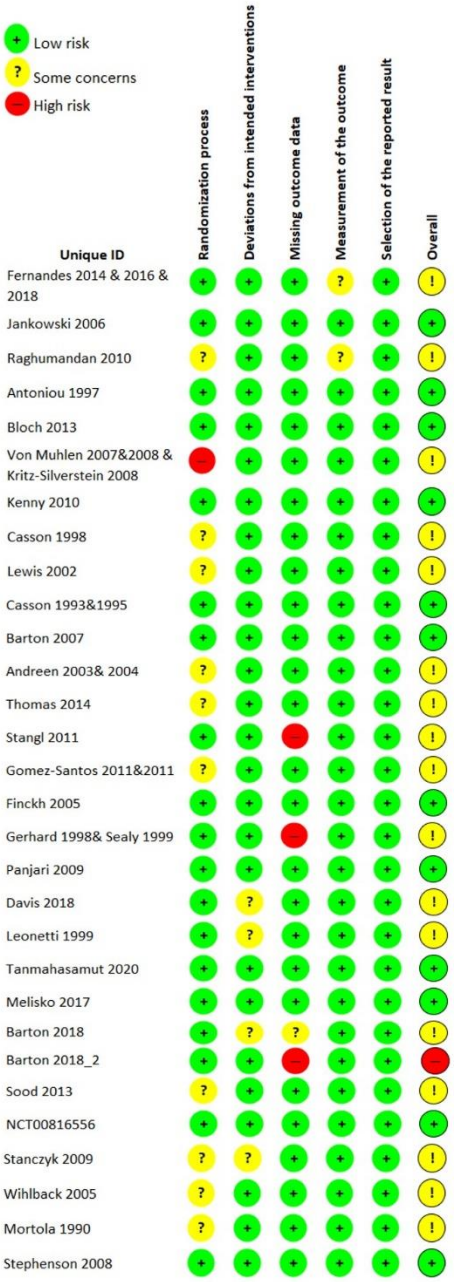

Low risk
Some concerns
High risk
Unique ID
Randomization process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome
Selection of the reported result
Overall
Fernandes 2014 & 2016 & 2018
Jankowski 2006
Raghumandan 2010
Antoniou 1997
Bloch 2013
Von Muhlen 2007&2008 & Kritz-Silverstein 2008
Kenny 2010
Casson 1998
Lewis 2002
Casson 1993&1995
Barton 2007
Andreen 2003& 2004
Thomas 2014
Stangl 2011
Gomez-Santos 2011&2011
Finckh 2005
Gerhard 1998& Sealy 1999
Panjari 2009
Davis 2018
Leonetti 1999
Tanmahasamut 2020
Melisko 2017
Barton 2018
Barton 2018_2
Sood 2013
NCT00816556
Stanczyk 2009
Wihlback 2005
Mortola 1990
Stephenson 2008

Figure S2

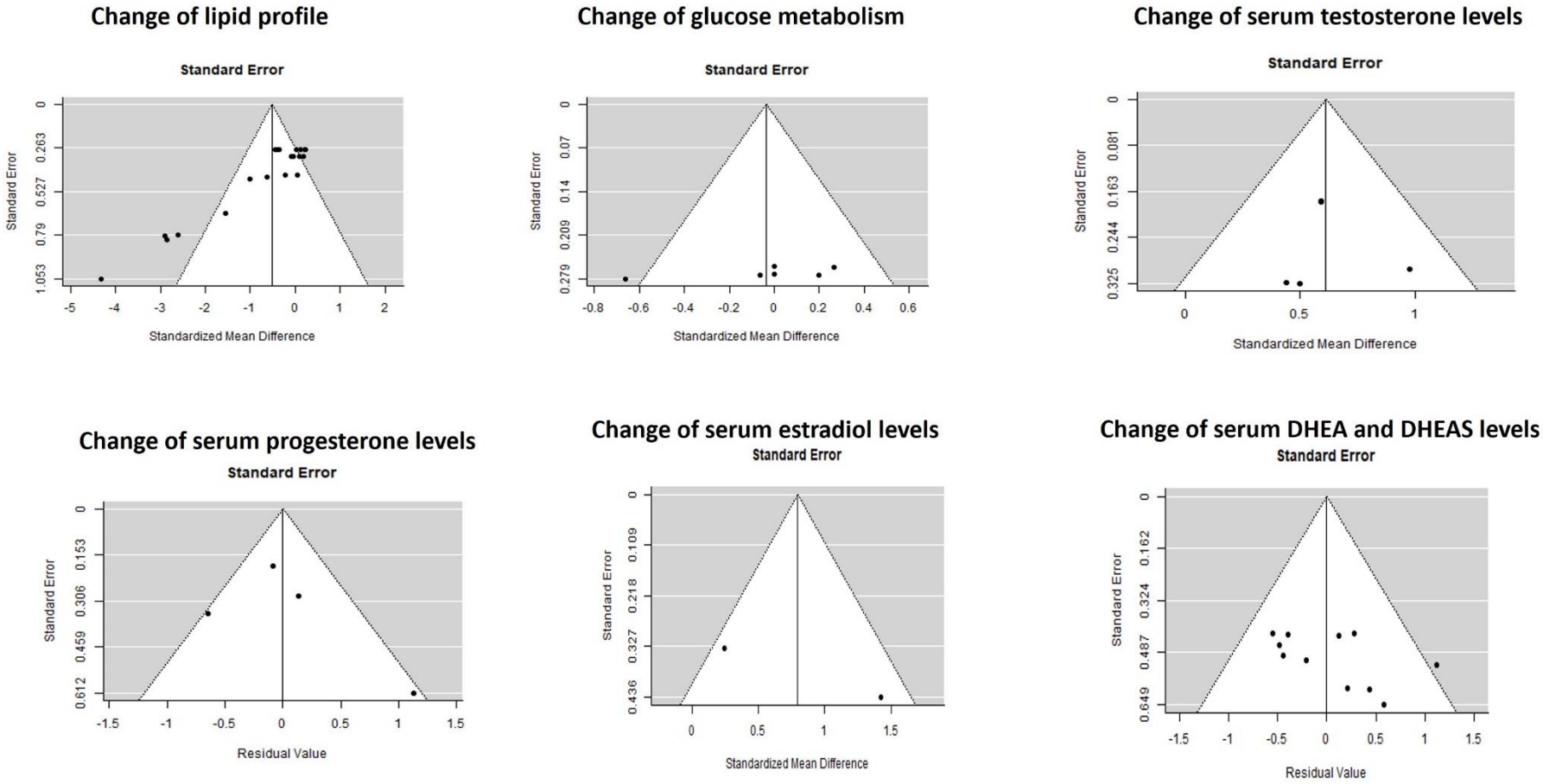
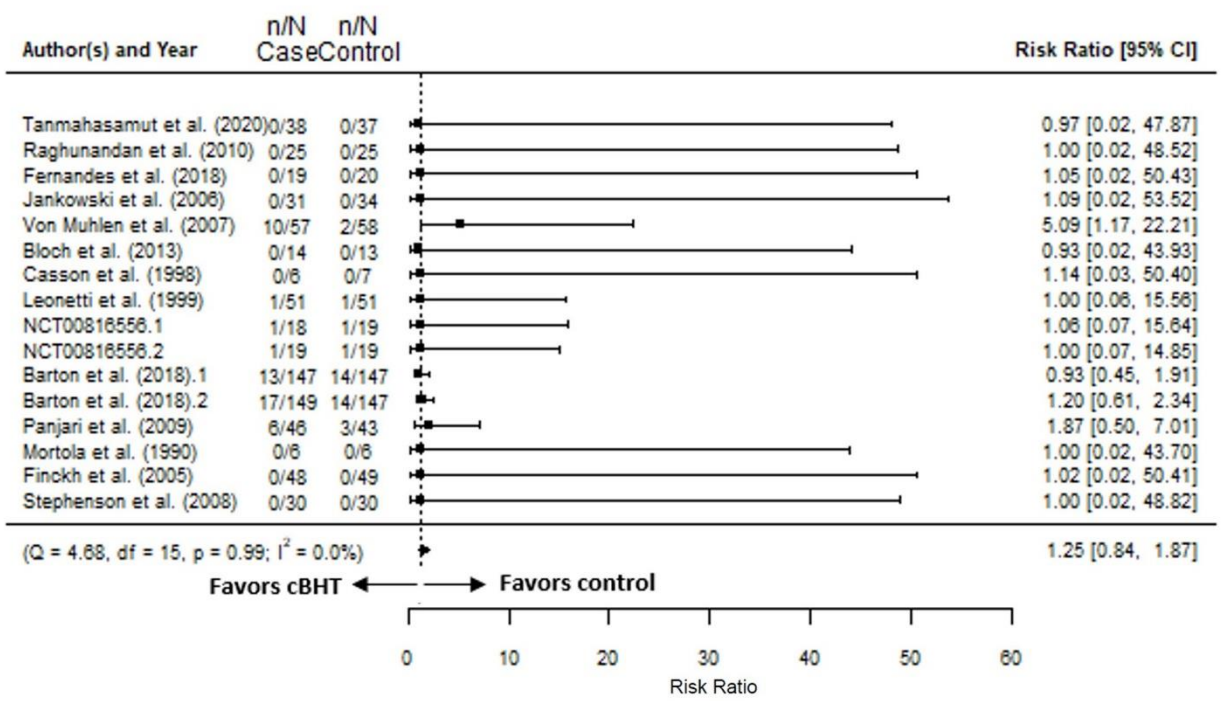

Change of lipid profile
Standard Error
Standard Error
Standardized Mean Difference
Change of glucose metabolism
Standard Error
Standard Error
Standardized Mean Difference
Change of serum testosterone levels
Standard Error
Standard Error
Standardized Mean Difference
Change of serum progesterone levels
Standard Error
Standard Error
Residual Value
Change of serum estradiol levels
Standard Error
Standard Error
Standardized Mean Difference
Change of serum DHEA and DHEAS levels
Standard Error
Standard Error
Residual Value

Figure S3

A


Author(s) and Year
n/N Case
n/N Control
Risk Ratio [95% CI]
Tanmahasamut et al. (2020) 0/38 0/37 0.97 [0.02, 47.87]
Raghunandan et al. (2010) 0/25 0/25 1.00 [0.02, 48.52]
Fernandes et al. (2018) 0/19 0/20 1.05 [0.02, 50.43]
Jankowski et al. (2006) 0/31 0/34 1.09 [0.02, 53.52]
Von Muhlen et al. (2007) 10/57 2/58 5.09 [1.17, 22.21]
Bloch et al. (2013) 0/14 0/13 0.93 [0.02, 43.93]
Casson et al. (1998) 0/6 0/7 1.14 [0.03, 50.40]
Leonetti et al. (1999) 1/51 1/51 1.00 [0.06, 15.56]
NCT00816556.1 1/18 1/19 1.06 [0.07, 15.64]
NCT00816556.2 1/19 1/19 1.00 [0.07, 14.85]
Barton et al. (2018).1 13/147 14/147 0.93 [0.45, 1.91]
Barton et al. (2018).2 17/149 14/147 1.20 [0.61, 2.34]
Panjari et al. (2009) 6/46 3/43 1.87 [0.50, 7.01]
Mortola et al. (1990) 0/6 0/6 1.00 [0.02, 43.70]
Finckh et al. (2005) 0/48 0/49 1.02 [0.02, 50.41]
Stephenson et al. (2008) 0/30 0/30 1.00 [0.02, 48.82]
(Q = 4.68, df = 15, p = 0.99; I² = 0.0%) 1.25 [0.84, 1.87]
Favors cBHT
Favors control
0
10
20
30
40
50
60
Risk Ratio

B

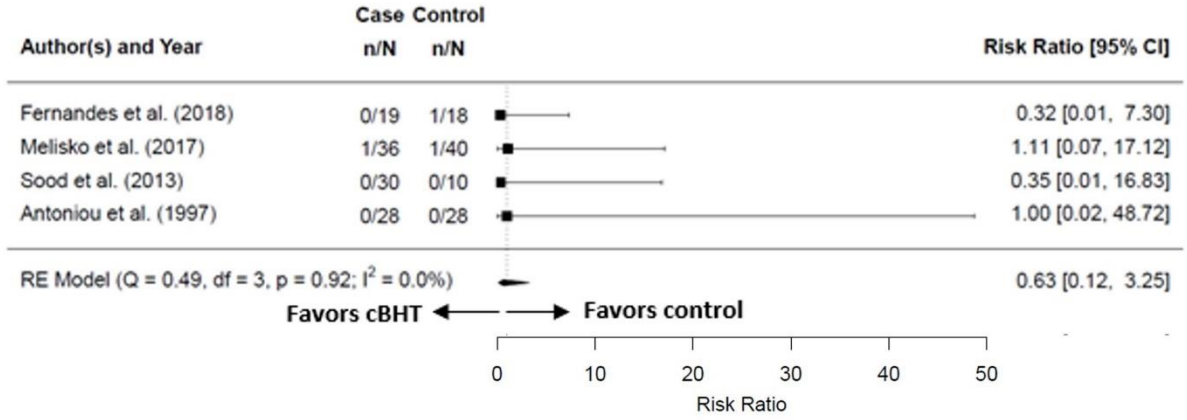

Case
Control
Author(s) and Year
n/N
n/N
Risk Ratio [95% CI]
Fernandes et al. (2018) 0/19 1/18 0.32 [0.01, 7.30]
Melisko et al. (2017) 1/36 1/40 1.11 [0.07, 17.12]
Sood et al. (2013) 0/30 0/10 0.35 [0.01, 16.83]
Antoniou et al. (1997) 0/28 0/28 1.00 [0.02, 48.72]
RE Model (Q = 0.49, df = 3, p = 0.92; I² = 0.0%) 0.63 [0.12, 3.25]
Favors cBHT
Favors control
0
10
20
30
40
50
Risk Ratio

Figure S4

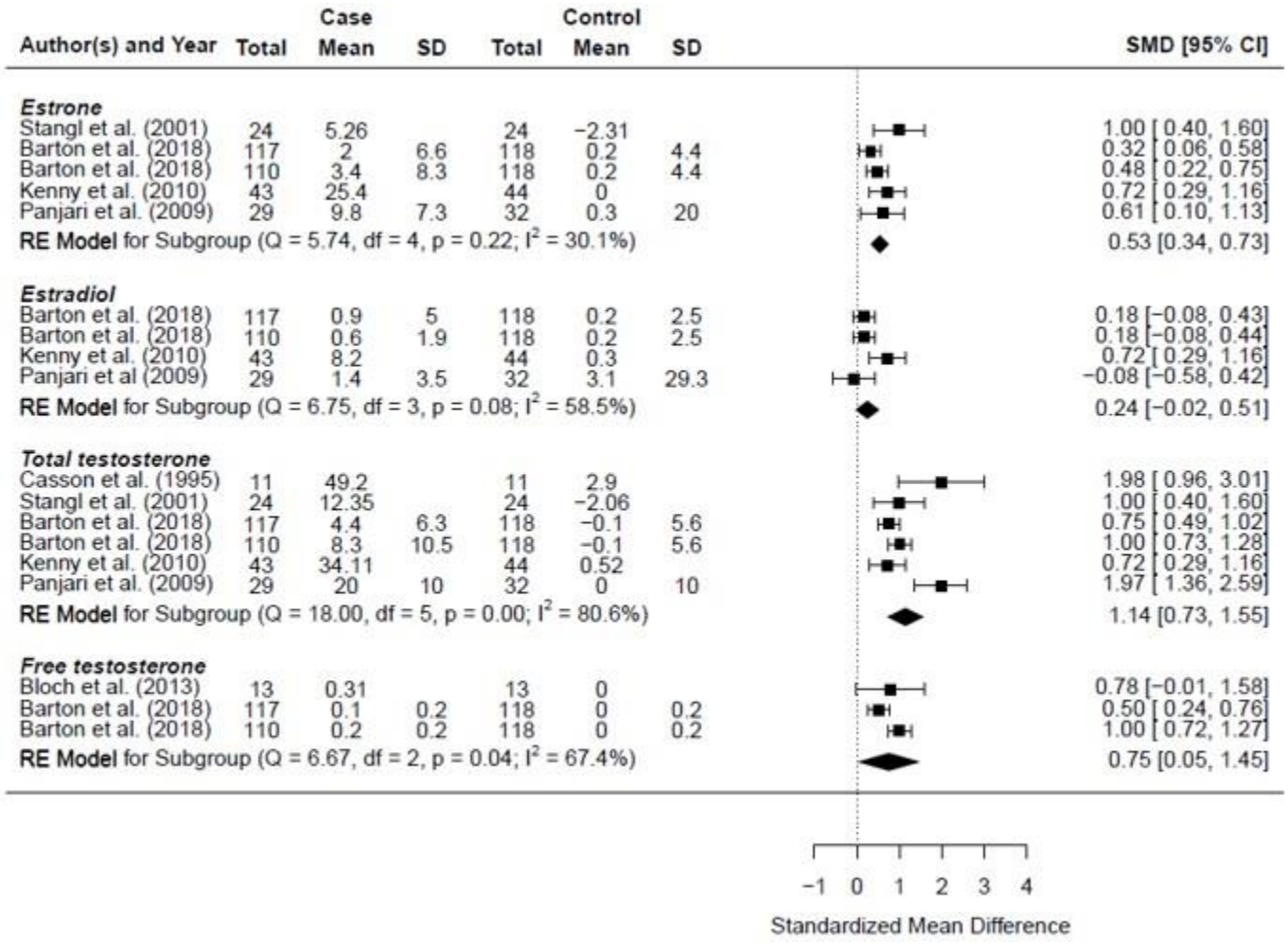
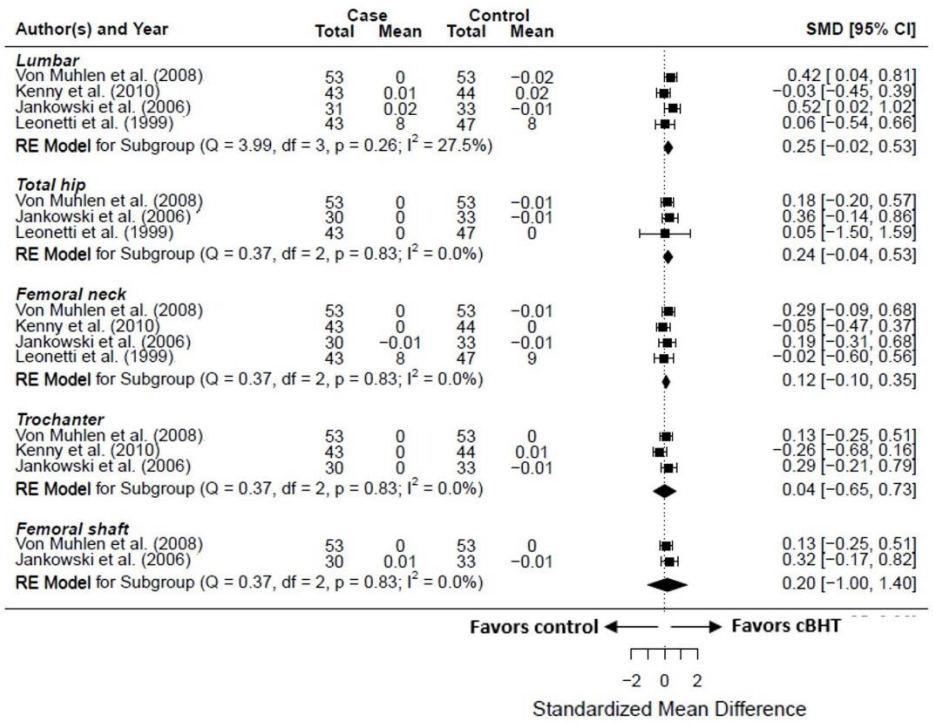

Author(s) and Year
Case
Control
Total
Mean
SD
Total
Mean
SD
SMD [95% CI]
Estrone
Stangl et al. (2001) 24 5.26 24 −2.31 1.00 [0.40, 1.60]
Barton et al. (2018) 117 2 6.6 118 0.2 4.4 0.32 [0.06, 0.58]
Barton et al. (2018) 110 3.4 8.3 118 0.2 4.4 0.48 [0.22, 0.75]
Kenny et al. (2010) 43 25.4 44 0 0.72 [0.29, 1.16]
Panjari et al. (2009) 29 9.8 7.3 32 0.3 20 0.61 [0.10, 1.13]
RE Model for Subgroup (Q = 5.74, df = 4, p = 0.22; I² = 30.1%) 0.53 [0.34, 0.73]
Estradiol
Barton et al. (2018) 117 0.9 5 118 0.2 2.5 0.18 [−0.08, 0.43]
Barton et al. (2018) 110 0.6 1.9 118 0.2 2.5 0.18 [−0.08, 0.44]
Kenny et al. (2010) 43 8.2 44 0.3 0.72 [0.29, 1.16]
Panjari et al (2009) 29 1.4 3.5 32 3.1 29.3 −0.08 [−0.58, 0.42]
RE Model for Subgroup (Q = 6.75, df = 3, p = 0.08; I² = 58.5%) 0.24 [−0.02, 0.51]
Total testosterone
Casson et al. (1995) 11 49.2 11 2.9 1.98 [0.96, 3.01]
Stangl et al. (2001) 24 12.35 24 −2.06 1.00 [0.40, 1.60]
Barton et al. (2018) 117 4.4 6.3 118 −0.1 5.6 0.75 [0.49, 1.02]
Barton et al. (2018) 110 8.3 10.5 118 −0.1 5.6 1.00 [0.73, 1.28]
Kenny et al. (2010) 43 34.11 44 0.52 0.72 [0.29, 1.16]
Panjari et al. (2009) 29 20 10 32 0 10 1.97 [1.36, 2.59]
RE Model for Subgroup (Q = 18.00, df = 5, p = 0.00; I² = 80.6%) 1.14 [0.73, 1.55]
Free testosterone
Bloch et al. (2013) 13 0.31 13 0 0.78 [−0.01, 1.58]
Barton et al. (2018) 117 0.1 0.2 118 0 0.2 0.50 [0.24, 0.76]
Barton et al. (2018) 110 0.2 0.2 118 0 0.2 1.00 [0.72, 1.27]
RE Model for Subgroup (Q = 6.67, df = 2, p = 0.04; I² = 67.4%) 0.75 [0.05, 1.45]
−1 0 1 2 3 4
Standardized Mean Difference

Figure S5

A


Author(s) and Year
Case Total Mean
Control Total Mean
SMD [95% CI]
Lumbar
Von Muhlen et al. (2008) 53 0 53 −0.02 0.42 [0.04, 0.81]
Kenny et al. (2010) 43 0.01 44 0.02 −0.03 [−0.45, 0.39]
Jankowski et al. (2006) 31 0.02 33 −0.01 0.52 [0.02, 1.02]
Leonetti et al. (1999) 43 8 47 8 0.06 [−0.54, 0.66]
RE Model for Subgroup (Q = 3.99, df = 3, p = 0.26; I² = 27.5%) 0.25 [−0.02, 0.53]
Total hip
Von Muhlen et al. (2008) 53 0 53 −0.01 0.18 [−0.20, 0.57]
Jankowski et al. (2006) 30 0 33 −0.01 0.36 [−0.14, 0.86]
Leonetti et al. (1999) 43 0 47 0 0.05 [−1.50, 1.59]
RE Model for Subgroup (Q = 0.37, df = 2, p = 0.83; I² = 0.0%) 0.24 [−0.04, 0.53]
Femoral neck
Von Muhlen et al. (2008) 53 0 53 −0.01 0.29 [−0.09, 0.68]
Kenny et al. (2010) 43 0 44 0 −0.05 [−0.47, 0.37]
Jankowski et al. (2006) 30 −0.01 33 −0.01 0.19 [−0.31, 0.68]
Leonetti et al. (1999) 43 8 47 9 −0.02 [−0.60, 0.56]
RE Model for Subgroup (Q = 0.37, df = 2, p = 0.83; I² = 0.0%) 0.12 [−0.10, 0.35]
Trochanter
Von Muhlen et al. (2008) 53 0 53 0 0.13 [−0.25, 0.51]
Kenny et al. (2010) 43 0 44 0.01 −0.26 [−0.68, 0.16]
Jankowski et al. (2006) 30 0 33 −0.01 0.29 [−0.21, 0.79]
RE Model for Subgroup (Q = 0.37, df = 2, p = 0.83; I² = 0.0%) 0.04 [−0.65, 0.73]
Femoral shaft
Von Muhlen et al. (2008) 53 0 53 0 0.13 [−0.25, 0.51]
Jankowski et al. (2006) 30 0.01 33 −0.01 0.32 [−0.17, 0.82]
RE Model for Subgroup (Q = 0.37, df = 2, p = 0.83; I² = 0.0%) 0.20 [−1.00, 1.40]
Favors control
Favors cBHT
−2 0 2
Standardized Mean Difference

B

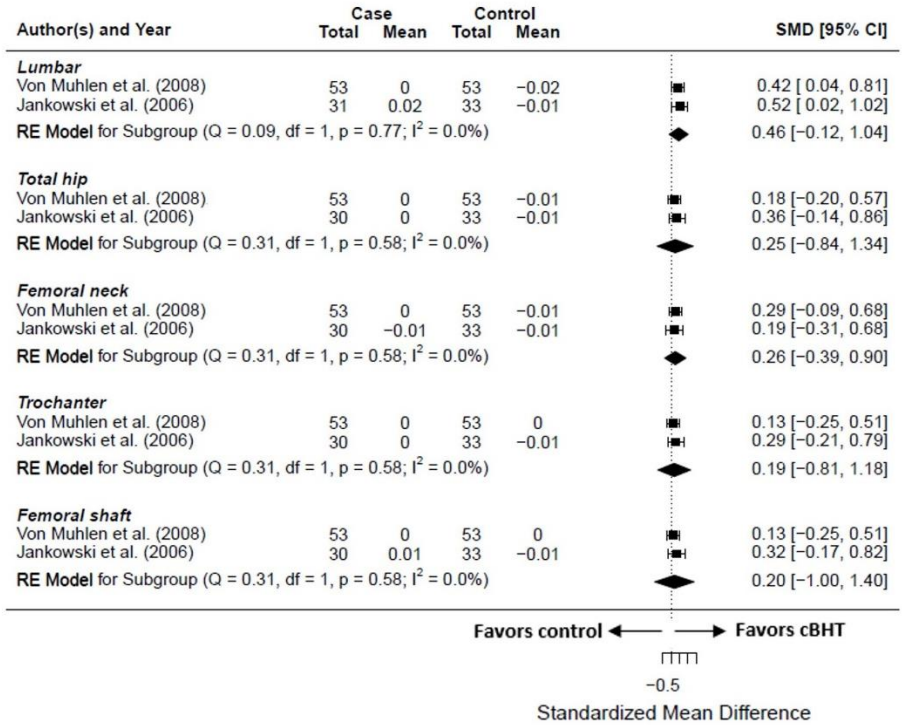
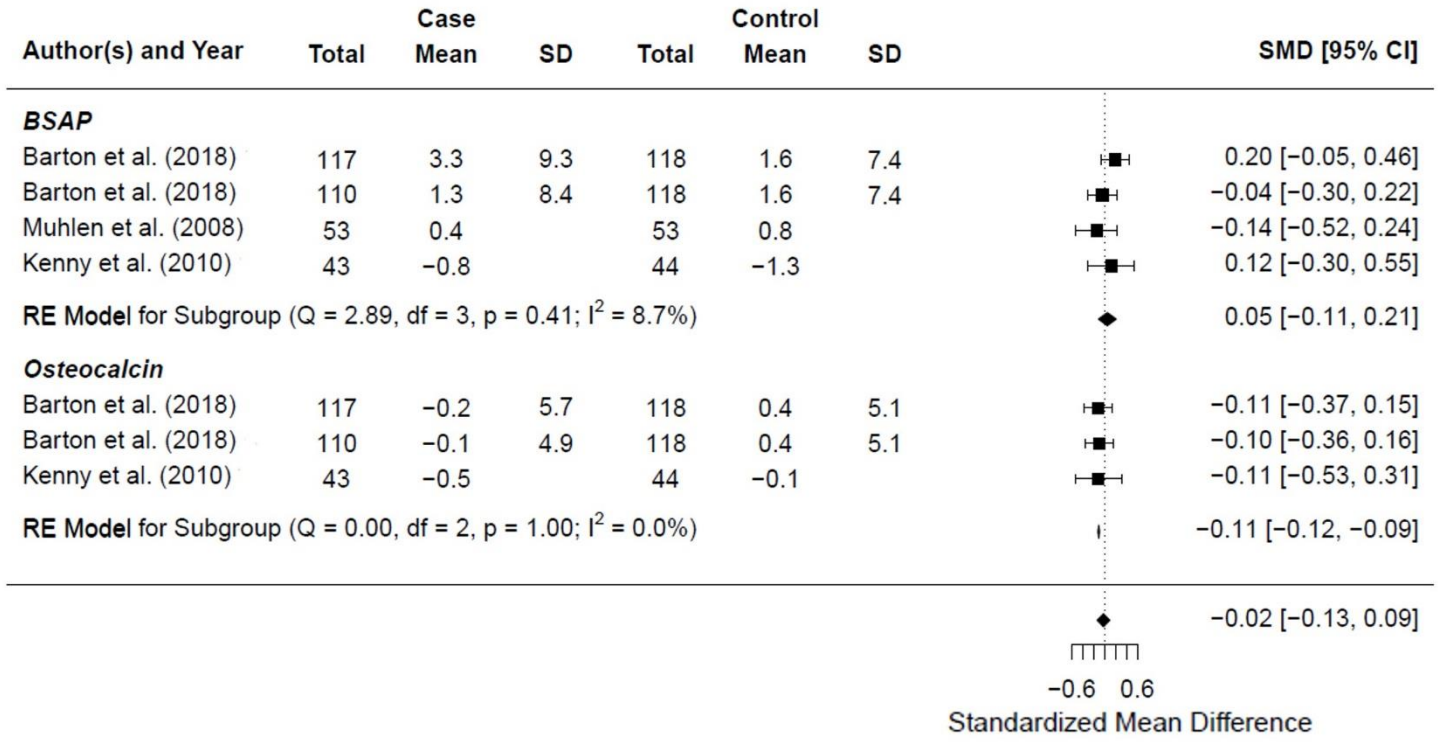

Author(s) and Year
Case Total Mean
Control Total Mean
SMD [95% CI]
Lumbar
Von Muhlen et al. (2008) 53 0 53 −0.02 0.42 [0.04, 0.81]
Jankowski et al. (2006) 31 0.02 33 −0.01 0.52 [0.02, 1.02]
RE Model for Subgroup (Q = 0.09, df = 1, p = 0.77; I² = 0.0%) 0.46 [−0.12, 1.04]
Total hip
Von Muhlen et al. (2008) 53 0 53 −0.01 0.18 [−0.20, 0.57]
Jankowski et al. (2006) 30 0 33 −0.01 0.36 [−0.14, 0.86]
RE Model for Subgroup (Q = 0.31, df = 1, p = 0.58; I² = 0.0%) 0.25 [−0.84, 1.34]
Femoral neck
Von Muhlen et al. (2008) 53 0 53 −0.01 0.29 [−0.09, 0.68]
Jankowski et al. (2006) 30 −0.01 33 −0.01 0.19 [−0.31, 0.68]
RE Model for Subgroup (Q = 0.31, df = 1, p = 0.58; I² = 0.0%) 0.26 [−0.39, 0.90]
Trochanter
Von Muhlen et al. (2008) 53 0 53 0 0.13 [−0.25, 0.51]
Jankowski et al. (2006) 30 0 33 −0.01 0.29 [−0.21, 0.79]
RE Model for Subgroup (Q = 0.31, df = 1, p = 0.58; I² = 0.0%) 0.19 [−0.81, 1.18]
Femoral shaft
Von Muhlen et al. (2008) 53 0 53 0 0.13 [−0.25, 0.51]
Jankowski et al. (2006) 30 0.01 33 −0.01 0.32 [−0.17, 0.82]
RE Model for Subgroup (Q = 0.31, df = 1, p = 0.58; I² = 0.0%) 0.20 [−1.00, 1.40]
Favors control
Favors cBHT
−0.5
Standardized Mean Difference

Figure S6


Author(s) and Year
Case
Total
Mean
SD
Control
Total
Mean
SD
SMD [95% CI]
BSAP
Barton et al. (2018) 117 3.3 9.3 118 1.6 7.4 0.20 [−0.05, 0.46]
Barton et al. (2018) 110 1.3 8.4 118 1.6 7.4 −0.04 [−0.30, 0.22]
Muhlen et al. (2008) 53 0.4 53 0.8 −0.14 [−0.52, 0.24]
Kenny et al. (2010) 43 −0.8 44 −1.3 0.12 [−0.30, 0.55]
RE Model for Subgroup (Q = 2.89, df = 3, p = 0.41; I² = 8.7%) 0.05 [−0.11, 0.21]
Osteocalcin
Barton et al. (2018) 117 −0.2 5.7 118 0.4 5.1 −0.11 [−0.37, 0.15]
Barton et al. (2018) 110 −0.1 4.9 118 0.4 5.1 −0.10 [−0.36, 0.16]
Kenny et al. (2010) 43 −0.5 44 −0.1 −0.11 [−0.53, 0.31]
RE Model for Subgroup (Q = 0.00, df = 2, p = 1.00; I² = 0.0%) −0.11 [−0.12, −0.09]
−0.02 [−0.13, 0.09]
−0.6
0.6
Standardized Mean Difference