

Review

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The effect of dehydroepiandrosterone (DHEA) supplementation on estradiol levels in women: a dose-response and meta-analysis of randomized clinical trials

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Short title: DHEA and Estradiol

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Abstract

Estradiol, an estrogen steroid hormone, serves as the dominant female hormone and its levels fluctuate during lifetime. In women, after the menopause, all estrogens and almost all androgens are locally developed in the peripheral tissues from dehydroepiandrosterone (DHEA). However, the effect of DHEA supplementation on estradiol levels in women is unclear as previously published data has resulted in conflicting findings. Thus, we conducted the present dose-response meta-analysis of randomized controlled trials (RCTs) evaluating the influence of DHEA on estradiol concentrations in women. The PubMed/Medline, Embase, Web of Science and Scopus databases were systematically searched for articles published on this topic until May 10, 2021. No time or language restrictions were applied. The data were expressed as weighted mean differences (WMDs) and 95% confidence intervals (CI), and a P-value of less than 0.05 was considered to be statistically significant. The pooled results were obtained using the generic inverse of variance method with a random effects model. A total of 21 arms, including 1223 participants (case=610, and control=613), reported estradiol concentrations as an outcome measure. The overall results demonstrated that estradiol significantly increased following the administration of DHEA (WMD: 7.02 pg/mL, 95% CI: 5.43, 8.62, $P=0.000$). The stratified analyses revealed that the elevation of estradiol concentrations was more pronounced in subjects aged ≥ 60 years old (WMD: 8.56 pg/mL, 95% CI: 6.97, 10.16, $I^2=94\%$) and in those receiving DHEA supplements for ≥ 26 weeks (WMD: 7.30 pg/mL, 95% CI: 6.28, 8.32, $I^2=61\%$). Moreover, estradiol levels increased significantly with DHEA dosages of 50 mg/day (WMD: 7.75 pg/mL, 95% CI: 9.12, 9.39, $I^2=94\%$) and when DHEA was prescribed to postmenopausal women (WMD: 7.61 pg/mL, 95% CI: 5.97, 9.24, $I^2=93\%$). This meta-analysis has provided a comprehensive overview of the effects of DHEA administration on circulating estradiol levels, far beyond the available evidence from different RCTs. Subsequent

on DHEA dosages of 50 mg/day and those receiving DHEA for ≥ 26 weeks registered a more pronounced elevation of the circulating estradiol levels.

Keywords: DHEA, estradiol, estrogen, women, meta-analysis, menopause.

Introduction

Dehydroepiandrosterone (DHEA) is an important prohormone secreted by the adrenals in large quantities in humans and other primates, but not in smaller species [1, 2]. DHEA is generated by the adrenal glands in humans and is employed by many tissues, including the brain, liver, kidneys, and gonads. Based on the tissue for which it is necessary, DHEA is metabolized to 5-androstene- $3\beta,17\beta$ -diol, 4-androstene-3,17-dione, testosterone, estrogen and other biologically active steroids [3-5] .

Estradiol, which is the dominant female hormone, fluctuates during lifetime and, at different times, during the menstrual cycle [6]. Estradiol (E2) serves as a strong feedback molecule between the ovaries and the hypothalamic neurons which generate the gonadotropin-releasing hormone (GnRH), and exerts both positive and negative regulatory actions on the GnRH synthesis and secretion [7]. In women, after the menopause, all estrogens and almost all androgens are locally developed in the peripheral tissues from DHEA, and have indirect effects on the bone structure, adiposity levels, muscles, insulin and glucose metabolisms, skin, libido and well-being [8, 9].

As estradiol is the dominant female hormone, maintaining its concentrations within normal limits, including during the menopause, is important for a normal status of health in women. Several trials have reported that the production of estradiol could be stimulated by DHEA [10-14]. Thus, it has been suggested that supplementation with DHEA could influence estradiol levels [14-16]. Nonetheless, the relationship between DHEA supplementation and estradiol levels remains

administration on estradiol concentrations remains unclear to this date [10, 12, 13, 17-19]. The discrepancies could be attributed to several items, such as the duration of intervention and the DHEA dosage, among others. In addition, before issuing a recommendation of DHEA supplementation to increase estradiol concentrations, we must keep in mind that a synthesis of high-quality, RCT-derived data is warranted to prevent any potential harms of such an intervention in women, as well as to identify the subjects who would benefit the most from DHEA prescription. Thus, we aimed to clarify the effects of DHEA supplementation on estradiol levels in females and we conducted the present dose-response meta-analysis of randomized controlled trials (RCTs) evaluating the influence of DHEA on estradiol concentrations in women.

Methods

This meta-analysis was executed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20, 21].

Search strategy

A literature search was computed to identify articles published before May 10, 2021, in the PubMed/Medline, Embase, Web of Science and Scopus databases. No restrictions regarding the publication year and language were applied. The following keywords and word combinations (both MeSH and non-MeSH) were employed: ("DHEA" OR "Prasterone" OR "Dehydroepiandrosterone" OR "DHEAS") AND ("clinical trials" OR "single-blind method" OR "double-blind method" OR "cross-over studies" OR "controlled trial" OR "RCT" OR "random allocation" OR "intervention studies" OR "intervention" OR "randomized" OR "randomised" OR "randomly" OR "random" OR "assignment" OR "placebo"). The search strategy is depicted in Supplementary Table 1. In addition, the reference lists of each identified publication were reviewed independently by two authors to generate more comprehensive results.

In order to be included in this meta-analysis, the papers had to meet following requirements: (1) the subjects in each study were women aged ≥ 18 years; (2) adult women were divided into an experimental group (receiving DHEA supplementation) and a control group (who did not receive DHEA); (3) the mean and standard deviation (SD) of estradiol concentrations were reported. The following exclusion criteria were applied: (1) editorials, commentaries, case reports, family-based studies and letters; (2) the subjects included in the studies were aged < 18 years; (3) the data from the trials was unobtainable; (4) the papers were not published in the English language.

The primary outcome of our systematic review and meta-analysis of RCTs was estradiol levels in females. The secondary outcomes included the influence of age, DHEA dosage, treatment duration and relation to menopause (pre/post-menopause) on the effects of DHEA supplementation on estradiol concentrations in women.

Data extraction

Two investigators independently extracted data from the included trials. Any disagreements were resolved by the supervising researcher. The following information was collected and recorded from each study: the publication year, the authors, the study design, the population, the number of cases and controls, the age of the participants, the treatment details (the use of DHEA, the time period of the study and the doses of DHEA), and the mean and SD of estradiol concentrations.

Quality assessment

To evaluate the quality of the analyzed manuscripts, we employed the Cochrane Collaboration's tool [22] which assesses: allocation concealment, generation of the allocation sequence, blinding of participants, masking of outcome assessors, incomplete follow-up, blinding of results assessment, selective reporting, and other biases (baseline incomparable). Finally, the risk of bias was classified into three levels: high-risk (> 1 one key criterion had a high-risk of bias), low-risk (no key domain had a high-risk of bias) and unclear.

All statistical analyses in this study were implemented using the Stata software (Stata Corp. College Station, Texas, USA). All the data were expressed as weighted mean differences (WMDs) and 95% confidence intervals (CI), and a P-value of less than 0.05 was considered to be statistically significant. The pooled results were obtained using the generic inverse of variance method with a random effects model. Heterogeneity among the trials was evaluated using the I^2 test ($I^2 > 50\%$ or a P -value < 0.10 signaled a significant heterogeneity among the trials). To identify the origin of the heterogeneity, we executed subgroup analyses across the mean age of the participants, the study duration, the DHEA dosage, and the type of the population. We performed a sensitivity analysis (by omitting each study and re-estimating the combined effect size) on the stability of the pooled results. The publication bias was assessed by funnel plots and using Egger's and Begg's tests. [23].

Results

Study selection and characteristics of the eligible trials

The total number of records initially identified using the search strategy was 6820. We then eliminated 2781 duplicates. A total of 3997 articles was deleted based on the screening of titles and abstracts. During the next stage, the full-texts of 62 trials were reviewed. Finally, 21 articles were included in the meta-analysis (**Figure 1**)[10-19, 24-34].

The characteristics of the 21 included RCTs are listed in **Table 1**. All the eligible studies reported the effects of the DHEA treatment on estradiol concentrations. Among the 21 studies, 10 were conducted in the United States of America (USA), 1 in Italy, 2 in Israel, 2 in Australia, 1 in Germany, 1 in Mexico, 1 in Sweden, 1 in Japan, 1 in Denmark and 1 in China. The analyzed papers were published between 1998 and 2019. The administrated dosage of DHEA varied between 35 mg to 270 mg, whilst the duration of the intervention ranged from 2 weeks to 12 months. The participants recruited in these RCTs were elder or postmenopausal women, healthy females or

HIV (human immunodeficiency virus) infection during the premenopausal period, primary Sjogren's syndrome, midlife-onset major and minor depression, or women undergoing in vitro fertilization by embryo transfer (IVT-ET). The risk of bias of each included study is shown in **Supplementary Table 2**.

Meta-analysis results

Impact of DHEA administration on estradiol concentrations

A total of 21 arms, with 1223 subjects (case=610, and control=613), described estradiol concentrations as an outcome measure. The overall results demonstrated that estradiol levels increased significantly following the administration of DHEA (WMD: 7.02 pg/mL, 95% CI: 5.10, 8.30, $P=0.000$), with a significant heterogeneity noted across the trials ($I^2=92.5\%$, $P=0.000$) (**Figure 2**).

Subgroup analyses

We subsequently stratified the studies based on the age of the participants and we observed that the elevation in estradiol concentrations was more pronounced in females aged ≥ 60 years (WMD: 8.56 pg/mL, 95% CI: 6.97, 10.16, $I^2=94\%$) as compared to those aged <60 years (WMD: 0.73 pg/mL, 95% CI: -5.85, 7.32, $I^2=86\%$) (**Table 2**). The subgroup analysis based on the DHEA dosage revealed that a dose of DHEA of 50 mg/day significantly increased estradiol levels (WMD: 7.75 pg/mL, 95% CI: 9.12, 9.39, $I^2=94\%$) *versus* a dose of >50 mg/day (WMD: 4.92 pg/mL, 95% CI: -4.85, 14.70, $I^2=90\%$) or <50 mg/day (WMD: 3.32 pg/mL, 95% CI: -5.52, 14.70, $I^2=39.8\%$). Based on the duration of the administration, the participants who received ≥ 26 weeks of DHEA exhibited higher estradiol levels at the end of the intervention (WMD: 7.30 pg/mL, 95% CI: 6.28, 8.32, $I^2=61\%$) as opposed to those who received DHEA for <26 weeks (WMD: 5.83 pg/mL, 95% CI: 0.17, 11.50, $I^2=96\%$). Moreover, DHEA raised estradiol concentrations only in postmenopausal

pg/mL, 95% CI: -8.31, 9.64, $I^2=80\%$) (**Table 2**).

Non-linear dose-response relationship between the DHEA dose, treatment duration and outcomes

The results demonstrated that DHEA significantly increased estradiol levels in the participants up to 80 years of age ($P=0.005$) (**Figure 3**).

Sensitivity analysis and Publication bias

The sensitivity analysis did not show a significant influence of any individual study on the combined effect sizes (**Figure 4**). We did not observe any evidence of publication bias in the visual inspection of the funnel plot (**Figure 5**). The Begg's ($P=0.904$) and Egger's ($P=0.608$) tests also confirmed the funnel plot results.

Discussion

This systematic review and dose-response meta-analysis was designed to investigate the impact of dehydroepiandrosterone (DHEA) supplementation on estradiol concentrations in women. The analysis of the 21 included RCTs revealed a significant increase in estradiol levels following the administration of DHEA, with a significant heterogeneity noted across the trials. DHEA was particularly effective in raising estradiol levels in postmenopausal women and in females aged ≥ 60 years, as well as when the dose of DHEA was ≥ 50 mg/d and when the duration of the intervention was ≥ 26 weeks. The body of evidence for this review is fairly extensive, with the inclusion of 21 RCTs and a total of 1223 participants, sufficient to detect a significant difference in the estradiol concentrations between the DHEA-supplemented group and the control group.

DHEA is a known androgen precursor that has no affinity for the androgen receptor but with in-vitro effects on several membrane-associated receptors [1], including direct binding to estrogen

in postmenopausal women resulted in less bone resorption [36, 37], bone resorption typically occurring after menopause as a consequence of the decrease in the levels of estradiol [38]. The potential benefit of DHEA supplementation would be to increase estrogen values to physiological levels that provide estrogenic effects, as opposed to supraphysiological estradiol levels that commonly cause endometrial stimulation and other adverse events [27]. Therefore, the development of endometrial cancer as a result of prolonged estrogen medication is believed to occur due to the activity of certain active estrogens, e.g. estradiol, that act as promoter substances by increasing the mitotic activity and possibly also by down-regulating of the defense system that targets the abnormal cell clones [39]. It is thus important to use low-dose DHEA (≤ 50 mg/day) which has been shown to cause a significant elevation in estradiol concentrations in postmenopausal women without causing any stimulating effect on the endometrium [40, 41]. This will eliminate the need for progestin therapy concomitant to the administration of DHEA, with the exception of elder women (aged ≥ 60 years) with long-term oral DHEA usage for ≥ 26 weeks, due to the effect of increasing the circulating levels of estradiol, as reported in this review. However, due to the significant impact of DHEA on the circulating concentrations of estradiol – which may promote tumorigenesis –, it should be noted that individuals taking DHEA supplements on a long-term basis may need to be monitored regularly for the development of hormone-sensitive cancer. Moreover, it should also be taken into consideration that DHEA supplementation should be cautiously prescribed. For example, women suffering from polycystic ovary syndrome also experience hyperandrogenism as part of this condition [42, 43]. Thus, DHEA supplementation in this patient subgroup is debatable. Fortunately, dietary interventions that can alleviate polycystic ovary syndrome traits are available [44-46].

Strength and limitations

of the effects of DHEA administration on circulating estradiol levels, far beyond the available evidence coming from different RCTs. Since our findings can potentially influence future clinical management approaches, this review represents a major addition to the literature. The evidence base before this manuscript lacked a summative, consensual assessment, and thus a quantitative evaluation was necessary, which we have now provided. Due to the rigorous methods used in this study (comprehensive searching, double-screening and data extraction, careful appraisal and analysis), biases are likely to be low. There are also a few limitations worth considering. The analyzed RCTs recruited patients with a myriad of health conditions, e.g. women undergoing IVF-ET [17], healthy postmenopausal or older women, older adults [10, 11, 14, 16, 18, 25, 28, 29, 31, 37], women suffering from anorexia nervosa [24], adrenal failure [12], mild to moderate cognitive impairment [26], HIV Infection [19], primary Sjogren's syndrome [15], and midlife-onset major and minor depression [30]. Although this permitted a larger number of studies and participants to be included in the evaluation, this could conceivably impact the mechanistic action and the generalizability of our results. Some RCTs included were small in sample size, as low as 15 participants [19], and it has been reported by Sterne et al. [47] that it is conceivable for small sample sizes to yield bigger effect sizes in intervention arms *versus* studies with larger participant pools. Nonetheless, this was out of the operational control of the meta-analysis. There are several factors which might have impacted on the heterogeneity of the results, e.g., the different types of DHEA supplements employed, the different settings and populations, thus we argue for a cautious interpretation of our results and a careful assessment of the clinical recommendation to administer DHEA supplements with the aim to increase estradiol concentrations. Moreover, the studies evaluated in this paper might suffer from significant sources of bias and the effect of the intervention was assessed by a few studies. Moreover, we did not register this systematic review and meta-analysis in the PROSPERO website.

This review has provided a comprehensive overview of the effect of DHEA administration on circulating estradiol levels, far beyond the available evidence in different RCTs. Subsequent subgroup analyses revealed that postmenopausal women, females aged 60 years and above, those on DHEA dosages of 50 mg/day and those receiving DHEA supplements for ≥ 26 weeks, exhibited a more pronounced elevation of the circulating estradiol concentrations. To the authors' knowledge, this study is the first meta-analysis to investigate the effects of DHEA administration on estradiol levels and, thus, represents a milestone for future practice and research to build upon. These studies are needed to understand the optimal DHEA doses for the treatment of postmenopausal women to avoid the potentially deleterious effects of excessive estradiol elevations. In the meantime, due to its significant impact on increasing circulating estradiol levels, DHEA supplementation may be an attractive option for improving or preserving bone health in older women.

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Highlights

1. DHEA supplementation was associated with increase in estradiol levels in women.
2. Estradiol levels increased significantly when 50 mg/day of DHEA were administered and when DHEA was prescribed in postmenopausal women.
3. The most notable increase in estradiol levels was detected in subjects aged ≥ 60 years and when DHEA was prescribed for ≥ 26 weeks

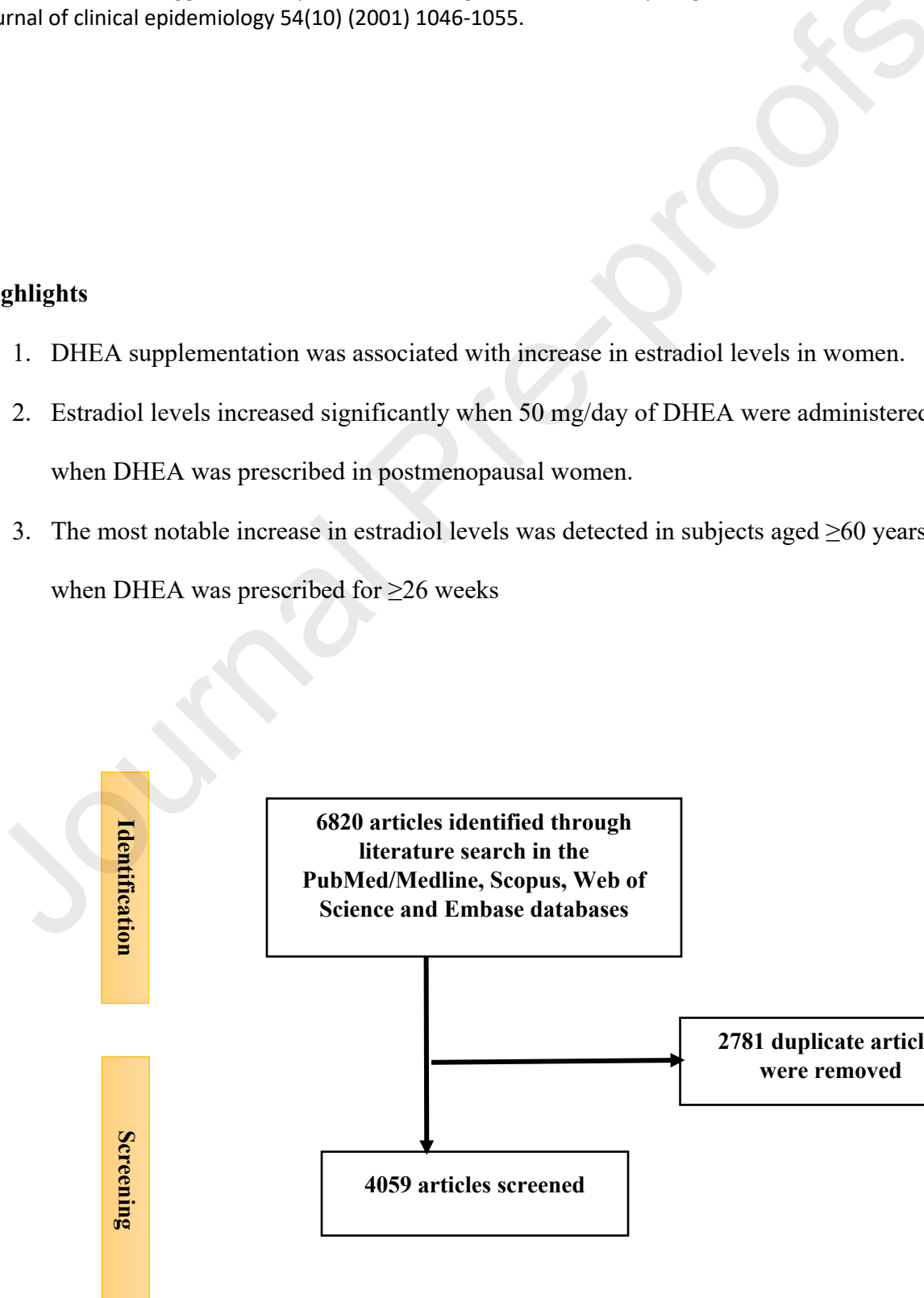
Identification

Screening

6820 articles identified through literature search in the PubMed/Medline, Scopus, Web of Science and Embase databases

2781 duplicate articles were removed

4059 articles screened



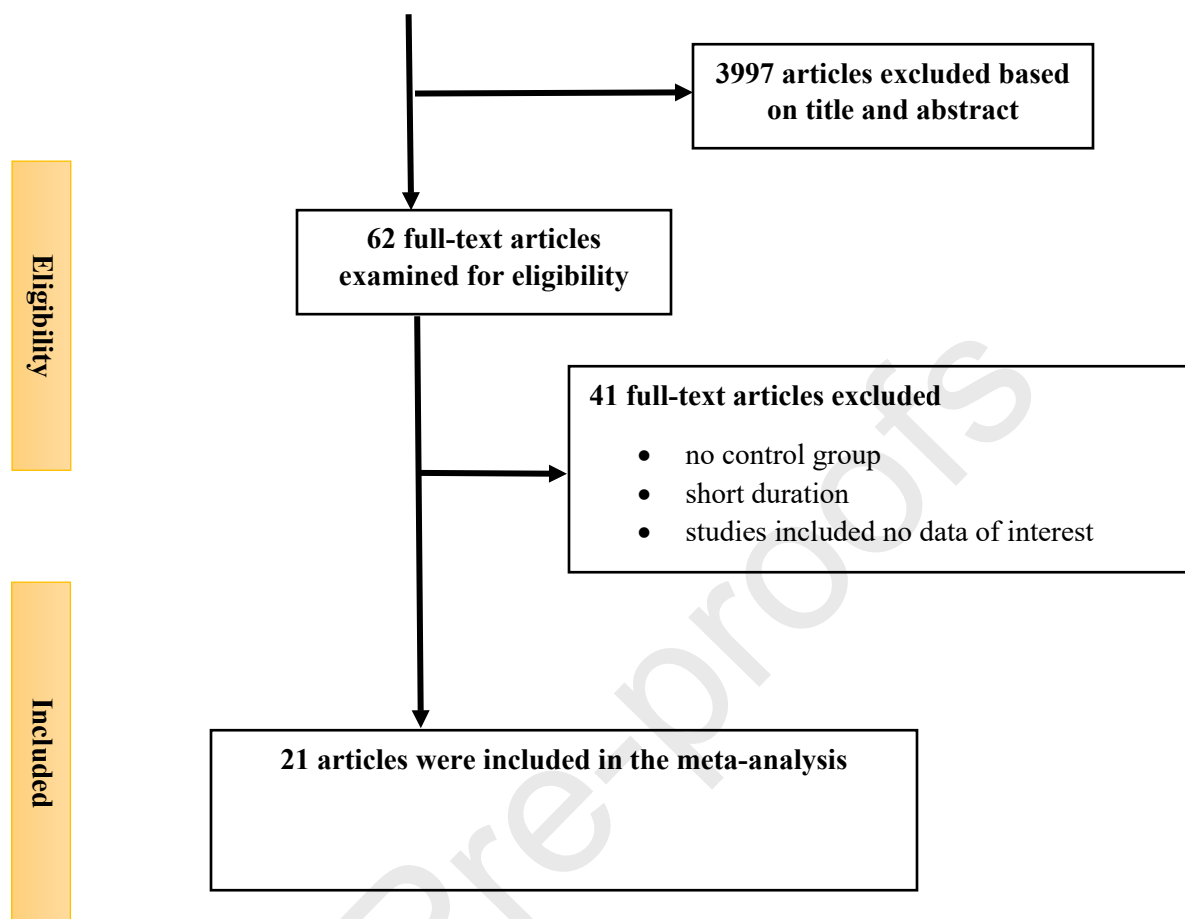


Figure 1. Flow-chart of the systematic review and meta-analysis evaluating the effects of dehydroepiandrosterone supplementation on estradiol levels.

Figure 2. Forest plot of the randomized controlled trials investigating the effect of dehydroepiandrosterone (DHEA) supplementation on serum estradiol concentrations.

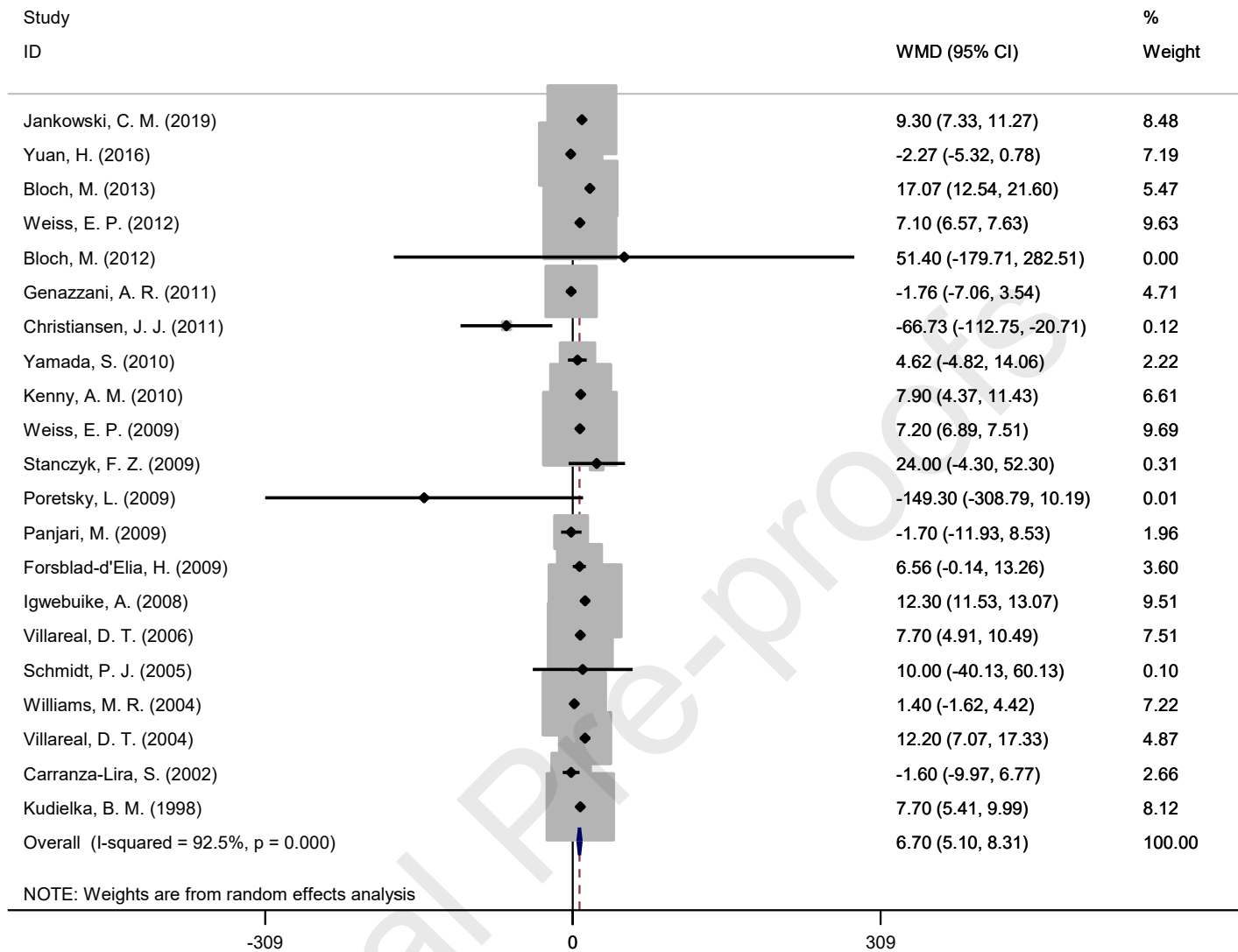
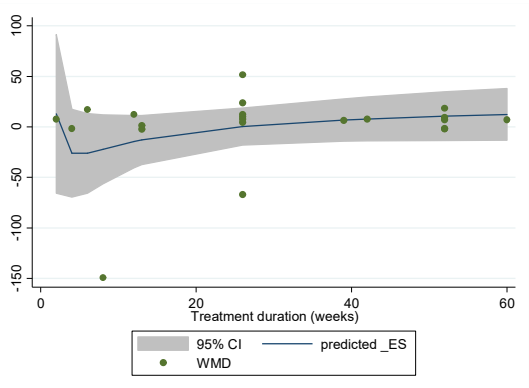
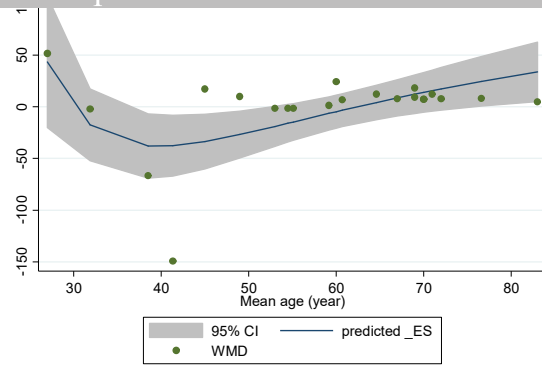
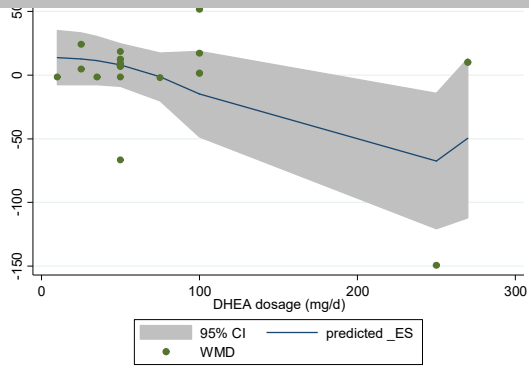


Figure 3. Non-linear dose-responses between the dehydroepiandrosterone DHEA dosage (mg/day) and the unstandardized mean difference in estradiol (pg/mL). The 95% confidence interval (CI) is depicted in the shaded regions.

P=0.245

P=0.005

P=0.160



$P=0.945$

$P=0.7500$

$P=0.115$

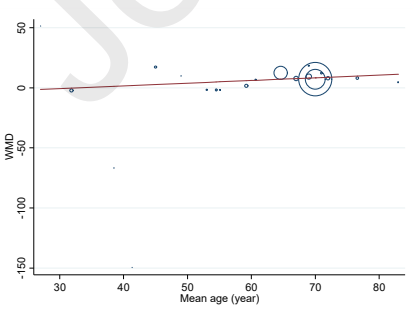
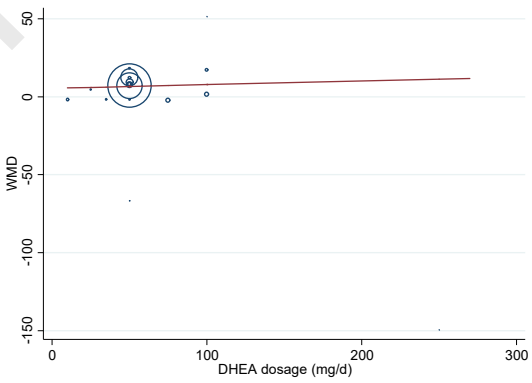
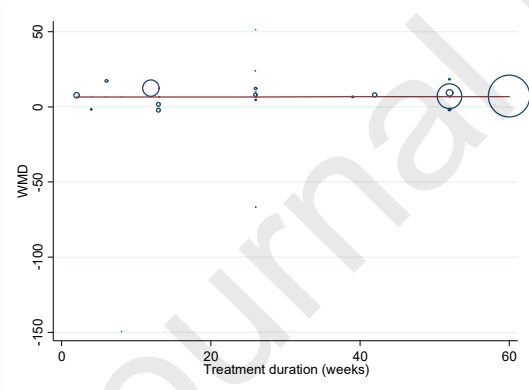
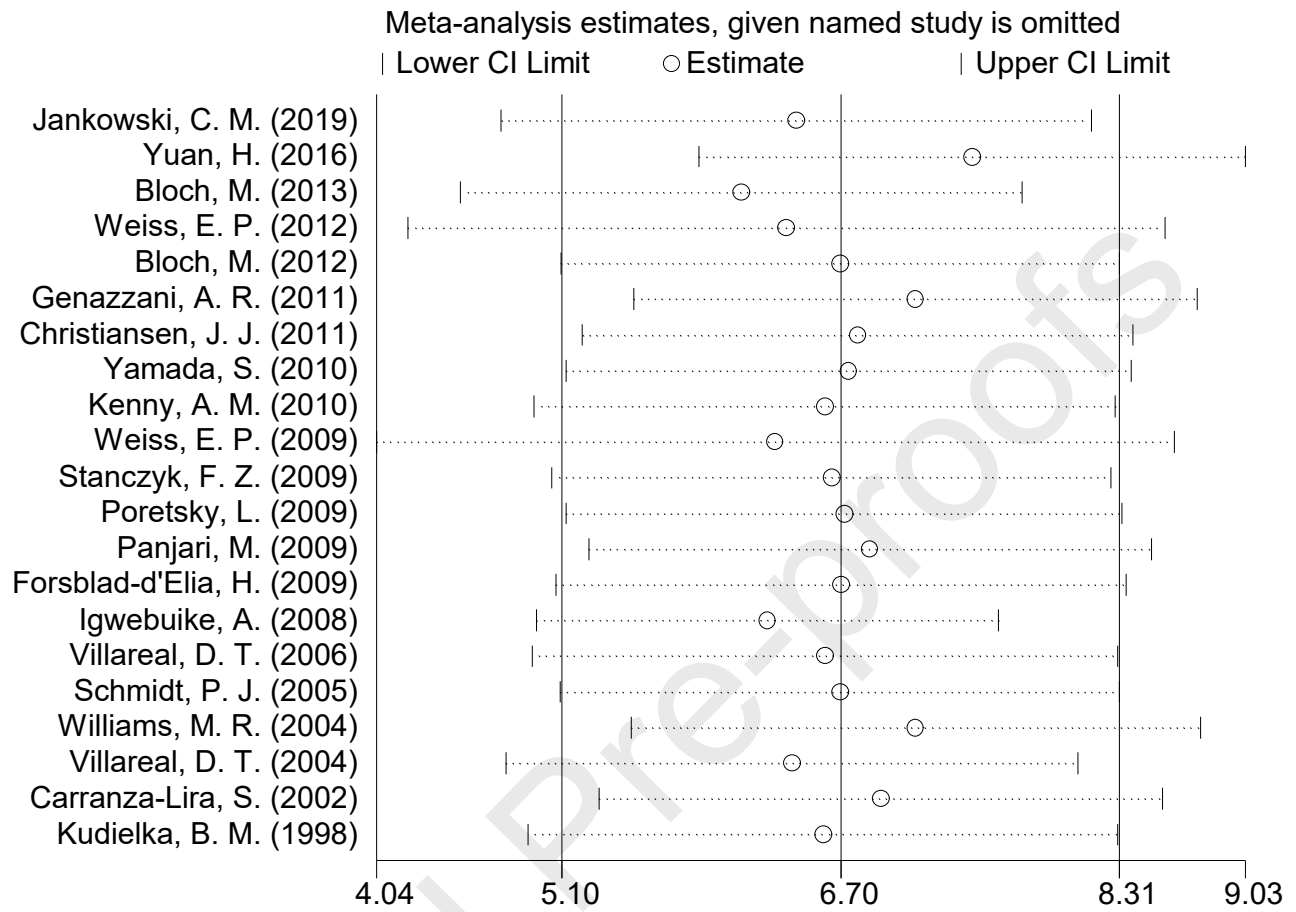
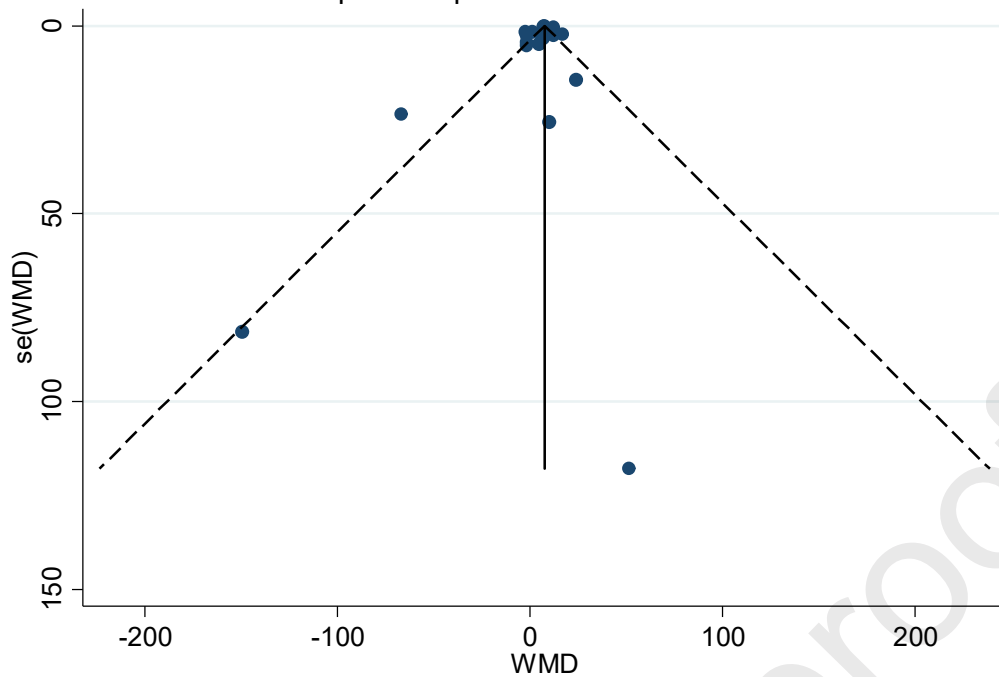


Figure 4. The results of the sensitivity analysis.**Figure 5.** Funnel plot of the weighted mean difference (WMD) versus the standard error (s.e.) of the WMD (P=0.608).

Funnel plot with pseudo 95% confidence limits

**Table 1.** Characteristics of eligible studies.

F, female. DHEA, dehydroepiandrosterone. mg/d, miligrams/day. IVF-ET, In Vitro Fertilization and Embryo Transfer. USA, United States of America.

| Author | Year | Country | Population | BMD | Participants' age (years) | Sample size DHEA/Placebo | Duration |
|------------------|------|---------|---------------------------------------|-------------------|---------------------------|--------------------------|-----------|
| Jankowski, C. M. | 2019 | USA | older adults | 0.845 ± 0.094 | 69 | 135/145 | 12 months |
| Yuan, H. | 2016 | China | patients undergoing IVF-ET | | 31.85 | 98/95 | 3 months |
| Bloch, M. | 2013 | Israel | postmenopausal women | | 45 | 13/13 | 6 weeks |
| Weiss, E. P. | 2012 | USA | older adults | | 70 | 20/22 | 12 months |
| Bloch, M. | 2012 | Israel | women diagnosed with anorexia nervosa | 1.0(1) | 27 | 13/8 | 6 months |

| Journal Pre-proofs | | | | | | | 12 mo |
|---------------------|------|-----------|---|------------------|----------|-------|-------|
| | | | women | | | | |
| Christiansen, J. J. | 2011 | Denmark | women diagnosed with adrenal failure | | 38.5 | 10/10 | 6 mo |
| Yamada, S. | 2010 | Japan | mild to moderate cognitive impairment | | 82 | 12/15 | 6 mo |
| Kenny, A. M. | 2010 | USA | frail older women | 0.85 0.14 | 76.59 | 43/44 | 6 mo |
| Weiss, E. P. | 2009 | USA | older adults | 0.896 6 0.022 | 70 | 58/58 | 12 mo |
| Stanczyk, F. Z. | 2009 | USA | postmenopausal women | | 55 to 65 | 7/7 | 6 mo |
| Poretsky, L. | 2009 | USA | premenopausal women with HIV Infection | | 41.33 | 9/6 | 8 we |
| Panjari, M. | 2009 | Australia | postmenopausal women | | 55.1 | 29/32 | 52 we |
| Forsblad-d'Elia, H. | 2009 | Sweden | postmenopausal women with primary Sjogrens syndrome | | 60.7 | 23/23 | 9 mo |
| Igwebuike, A. | 2008 | USA | postmenopausal women | | 64.59 | 17/17 | 12 we |
| Villareal, D. T. | 2006 | USA | elderly women and men | | 72 | 29/27 | 10 mo |
| Schmidt, P. J.(b) | 2005 | USA | midlife-onset major and minor depression | | 49 | 23/23 | 6 we |
| Williams, M. R. | 2004 | Australia | healthy postmenopausal women | | 59.2 | 18/18 | 3 mo |
| Villareal, D. T.(b) | 2004 | USA | elderly women | | 71 | 13/14 | 6 mo |

| Journal Pre-proofs | | | | | | | 1 mo |
|--------------------|------|---------|--------------------------|--|----|-------|------|
| | | | postmenopausal women | | | | |
| Kudielka, B. M. | 1998 | Germany | healthy elderly subjects | | 67 | 18/18 | 2 we |

Table 2. Subgroup analysis to assess the effect of DHEA supplementation on estradiol levels.

| Subgrouped by | Number of trials | WMD 95% CI | | | P-value | P for heterogeneity |
|---|------------------|------------|-------|-------|---------|---------------------|
| | | | | | | |
| Age (years) | | | | | | |
| <60 | 10 | 0.73 | -5.85 | 7.32 | 0.827 | 0.000 |
| ≥60 | 10 | 8.56 | 6.97 | 10.16 | 0.000 | 0.000 |
| Dosage | | | | | | |
| <50 mg | 3 | 3.32 | -5.52 | 12.16 | 0.000 | 0.190 |
| 50 mg | 12 | 7.75 | 6.12 | 9.39 | 0.462 | 0.000 |
| >50 mg | 6 | 4.92 | -4.85 | 14.70 | 0.324 | 0.000 |
| Intervention duration (weeks) | | | | | | |
| <26 | 7 | 5.83 | 0.17 | 11.50 | 0.003 | 0.043 |
| ≥26 | 13 | 7.30 | 6.28 | 8.32 | 0.000 | 0.000 |
| Health status | | | | | | |
| Postmenopausal women | 10 | 7.61 | 5.97 | 9.24 | 0.000 | 0.000 |
| Premenopausal women | 10 | 0.66 | -8.31 | 9.64 | 0.884 | 0.000 |
| DHEA, dehydroepiandrosterone. mg, milligrams. WMD, weighted mean difference. CI, confidence interval. | | | | | | |