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PII: S0965-2299(20)31887-2

DOI: <https://doi.org/10.1016/j.ctim.2020.102620>

Reference: YCTIM 102620

To appear in: *Complementary Therapies in Medicine*

Received Date: 25 April 2020

Revised Date: 10 November 2020

Accepted Date: 11 November 2020

Please cite this article as: Hu Y, Wan P, An X, Jiang G, Impact of dehydroepiandrosterone (DHEA) supplementation on testosterone concentrations and BMI in elderly women: A dose-response meta-analysis of randomized controlled trials, *Complementary Therapies in Medicine* (2020), doi: <https://doi.org/10.1016/j.ctim.2020.102620>

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Impact of dehydroepiandrosterone (DHEA) supplementation on testosterone concentrations and BMI in elderly women: A dose-response meta-analysis of randomized controlled trials

Short title: DHEA and testosterone in the women elderly

Short title: DHEA effect on testosterone levels and BMI in elderly women

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Highlights

- Overall results demonstrated that testosterone levels increased significantly after DHEA administration in elderly women.
- DHEA administration significantly decreased BMI.

Abstract

Background: Despite the fact that numerous clinical studies have evaluated the positive effects of dehydroepiandrosterone (DHEA) supplementation on testosterone concentrations and on the body mass index (BMI), more evidence is needed to certify that DHEA is a BMI-reducing agent in the elderly. This meta-analysis aims to clarify the various incompatible results and investigate the impact of DHEA supplementation on serum testosterone levels and lean body mass in elderly women.

Methods: Four scientific databases (EMBASE, PubMed/MEDLINE, Scopus and Web of Science) were searched from inception until 20 August 2020 for trials comparing DHEA with placebo. Results were presented as weighted mean differences (WMDs) and 95% confidence intervals (CIs) based on the random effects model (DerSimonian-Laird approach).

Results: Nine arms with 793 subjects reported testosterone as an outcome measure. The overall results demonstrated that testosterone levels increased significantly after DHEA administration in elderly women (WMD: 17.52 ng/dL, 95% CI: 6.61, 28.43, $P=0.002$). In addition, DHEA administration significantly decreased the BMI (WMD:-0.39 kg/m², $I^2=0.0\%$).

Conclusion: The results of the current meta-analysis support the use of DHEA supplementation for increasing testosterone concentrations in elderly women.

Keywords: dehydroepiandrosterone; DHEA; women, testosterone; BMI; elderly

Introduction

Dehydroepiandrosterone (DHEA) and its sulfated form, i.e. DHEAS, have the highest plasma concentrations among steroid hormones(1). In humans, DHEA(S) is secreted by the zona reticularis of the adrenal cortex and its production starts from puberty and peaks at the age of 20. After the age of 25, a rapid reduction emerges and, by the age of 75, its plasma levels are 80% less than those measured at the age of 25 (2). Until now, several effects of DHEA on the human health have been identified, e.g. DHEA reduces inflammation and stimulates or improves cognition, memory, insulin sensitivity and the immune system (3, 4). Studies have revealed that the age-related decline in DHEA levels might be associated with various disorders(5). Thus, DHEA supplementation has been investigated, with recent reports showing its efficacy in enhancing psychological and physical well-being, muscle strength, sexual function, and insulin sensitivity (6-10). Moreover, DHEA replacement prevents bone loss and improves bone mass density (BMD), decreases fat mass and body weight (11-13). Since DHEA is the precursor of testosterone, higher levels of testosterone as result of DHEA supplementation can be expected. Testosterone concentrations decrease with age and contribute to reduced muscle mass and bone density, impaired hair growth and sexual dysfunction (14, 15). Thus, body composition differs following changes in the hormonal status (16). For instance, due to age-dependent decreases in DHEA and testosterone concentrations, the loss of bone and muscle mass as components of free fat mass are common consequences. In order to alleviate the rate of bone and muscle mass loss, keeping DHEA levels in “youthful” ranges has been suggested as a beneficial strategy(17). Lean body mass is described as the total body mass without the fat mass, mainly consisting of bone and muscle mass(18). The best evidence of DHEA supplementation is related to BMD accretion and improvement of muscle mass and strength *via* DHEA’s influence on lean body mass in older adults (19, 20). Despite the fact that numerous clinical studies have evaluated the positive effects of

DHEA consumption on the aforementioned body components, more evidence is needed to deduce that DHEA promotes lean body mass in the elderly. This meta-analysis aims to clarify the various incompatible results and investigate the impact of DHEA supplementation on serum testosterone levels and lean body mass in the elderly women.

Methods

This meta-analysis was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(21).

Search strategy

Four scientific databases (EMBASE, PubMed/MEDLINE, Scopus and Web of Science) were searched from inception until 20 August 2020 for trials comparing DHEA with placebo. The search terms "Dehydroepiandrosterone" OR "DHEA" OR "Prasterone" OR "DHEAS and old people" OR "elderly" OR "aged" OR "older people" OR "old population" were used without any language restrictions. The references of the published meta-analyses and of the included trials were reviewed to identify other potentially eligible papers.

Eligibility criteria

The eligibility criteria for the selection of eligible trials were constructed according to the PICOS (participants, interventions, comparisons, outcomes, and study designs) framework.

Participants. Publications included studies conducted in humans, namely elderly women (≥ 60 years old).

Interventions and comparisons. Interventions and comparators were DHEA and placebo, respectively.

Outcomes. Clinical outcomes were testosterone, BMI, lean body mass (LBM), and body weight.

Study design. Randomized controlled trials (RCTs) reporting at least 1 predefined result were chosen.

The exclusion criteria were as follows: (1) non-English publications; (2) non-clinical trials (reviews, letters, case reports, meeting notices and expert experience reports); (3) studies without a control group; (4) trials containing insufficient data; and (5) animal experiments.

Data extraction

The data of interest from the eligible articles was extracted independently by two investigators using a standard Microsoft Excel spreadsheet, which included the following information: first author, publication year, country where the trial was executed, mean age of the sample, sex of the participants, sample size of the DHEA group and placebo, duration of DHEA administration (weeks), DHEA doses, mean and standard deviation (SD) of testosterone levels, mean and SD of LBM, mean and SD of BMI and mean and SD of body weight. Discrepancies between the two investigators were resolved through consensus with the senior author.

Quality assessment

The quality of the included publications was evaluated for the risk of bias using the *Cochrane Handbook*. (i) selection bias (condition allocation through random sequence generation); (ii) allocation bias (concealment of condition allocation); (iii) performance bias (blinding of participants and study personnel to condition); (iv) detection bias (blinding of outcome assessment); (v) attrition bias (incomplete outcome data); and (vi) reporting bias (selective outcome reporting of results). Each domino was ranked as “unclear deviation risk” or “low deviation risk,” or “high deviation risk” and rated as “good, fair, and poor based on the AHRQ (Agency for Healthcare Research and Quality) standards”(22).

Statistical methods

Results were presented as weighted mean differences (WMDs) and 95% confidence intervals (CIs) based on the random effects model (DerSimonian-Laird approach). We used the Stata program for all statistical analyses. Data was combined using the generic inverse variance method with random effects model (DerSimonian-Laird approach) and described as WMDs with 95% CIs. When the mean and SD of the data was specified in a different format, we estimated them using standard calculations (23, 24). Heterogeneity was evaluated by applying the I-squared statistic and subgroups analyses were conducted to find possible sources of heterogeneity. We performed a sensitivity analysis of effect sizes by the sequential removal of each trial. Publication bias for the primary efficacy outcome was evaluated using the Egger's test and the visual appraisal of funnel plots (25).

Results

Study selection and characteristics of the eligible trials

Among 2,032 records included in our initial search, 9 publications were included in our meta-analysis based on the inclusion criteria (**Figure 1**) (26-34). The characteristics of the included studies are presented in Table 1. The mean age of the participants was of 68 years. The eligible trials were published between 2006 and 2019. The treatment durations were variable between the included trials, ranging from 4 to 52 weeks. The studies were conducted in different countries: Italy, The United States, and Sweden. The dosage of DHEA varied between 50 to 90 mg. The risk of bias and the methodological quality of the eligible trials are described in **Supplementary Table 1**.

Meta-analysis results

Impact of DHEA administration on testosterone levels in elderly women

Nine arms with 793 subjects (case=376, and control=417) reported testosterone levels as an outcome measure. The overall results demonstrated that testosterone levels increased significantly after DHEA administration (WMD: 17.52 ng/dL, 95% CI: 6.61, 28.43, $P=0.002$), with a significant heterogeneity across the trials ($I^2=98\%$, $P=0.000$) (**Figure 2**). The sensitivity analysis did not detect a significant influence of any of the studies in particular on the overall results (**Supplementary Figure 1**).

Impact of DHEA administration on LBM in elderly women

Three arms with 186 subjects (case=93, and control=93) reported LBM as an outcome measure. The overall results demonstrated that LBM increased significantly after DHEA administration (WMD: 0.68 Kg, 95%CI: 0.31, 1.05, $P=0.000$), with no significant heterogeneity across the trials ($I^2=58.8\%$, $P=0.089$) (**Figure 3**).

Impact of DHEA administration on BMI in the elderly

Two arms (33, 34) with 93 subjects (case=47, and control=46) reported BMI as an outcome measure. The overall results demonstrated that BMI decreased significantly after DHEA administration (WMD: -0.39 kg/m², 95% CI: -0.46,-0.33, $P=0.000$), with no significant heterogeneity across the trials ($I^2=0.0\%$, $P=0.712$).

Impact of DHEA administration on body weight in the elderly

Two arms (33, 34) with 93 subjects (case=47, and control=46) reported body weight as an outcome measure. The overall results demonstrated that body weight decreased significantly after DHEA administration (WMD: -0.46 kg, 95% CI: -2.90, 1.98, $P=0.711$), with a significant heterogeneity across the trials ($I^2 = 90\%$, $P=0.004$).

Publication bias

The evaluation of the publication bias by the Egger's test did not detect any evidence of publication bias in the current study. The visual inspection of the funnel plot also revealed the same result (**Figure 4**).

Discussion

The overarching aim of this systematic review and dose-response meta-analysis was to investigate the impact of DHEA supplementation on serum testosterone levels and body weight, BMI and LBM in the elderly women. Given the increasing prevalence of low serum testosterone in the elderly (35, 36) and its debilitating effects on the quality of life (8), understanding the potential contributing or mediating factors that lead to this decrease is of paramount importance. This meta-analysis found a significant and direct relation between DHEA supplementation and testosterone levels in elderly women. An improvement of the BMI was also observed.

In this study, testosterone therapy was associated with changes in the body composition *via* a decrease in BMI and an increase in lean mass, but no difference in body weight *versus* placebo was seen, suggesting that patients had some perceived benefit from the treatment due to the possible favorable effects of the reduction of fat mass. Marin et al. (37, 38) reported that

testosterone supplementation with low to low-normal testosterone concentrations is associated with a significant reduction in visceral fat, plasma insulin levels, and blood glucose concentrations. Moreover, it is likely that the reduction of the BMI might have alleviated the impact of the numerous comorbidities encountered in the elderly population, e.g. cardiovascular and metabolic disorders and also certain types of solid or blood cancers, mainly by reducing body fat which is a source of pro-inflammatory adipo-cytokines and reactive oxygen species (39-44). However, despite the fact that several natural products and supplements have shown promising effects on decreasing the BMI and improving obesity indices, physicians should keep an eye on the potential risks associated with the consumption of over-the-counter drugs and supplements which might lead to adverse effects or even drug-drug or food-drug interactions, especially in patients who are already exposed to polypharmacy (45-50).

If the studies had used a higher dose of oral testosterone, we could have possibly detected an effect on muscle mass, but the dosage of DHEA was limited to 50-90 mg. However, a comparison of muscle strength may not yield clear results because there was an apparent increase in muscle strength in both the placebo and the treatment groups, raising the possibility that a neural learning effect may confound the data. Another possible explanation for this result is the lack of data to assess whether the elderly in the studies were suffering from sarcopenia at the beginning of the assessments in the analyzed studies (51).

The primary strength of this study was that our meta-analysis provided a comprehensive overview of the effects of DHEA supplementation in the elderly. We were also able to conduct stratified analyses based on both the duration of the supplementation and the dosage, in addition to evaluating DHEA's effects on body weight, BMI and LBM, thereby providing foresight into the expected outcomes based on such information. Notwithstanding, the current study has some

limitations. The analyses were not restricted to solitarily include patients of one type, e.g. elderly with and without sarcopenia were included. Consequently, this allowed for a larger number of studies and participants with sarcopenia to be included in the analyses, but this could have also affected the mechanism of action of DHEA. Some of the included trials were small, having as little as 17 participants. Thus, it is possible that the investigations with small study samples might have reported bigger effect sizes in the intervention arms than the studies with more participants. Nevertheless, this was out of the operational control of this meta-analysis.

Conclusion

The results of current meta-analysis support the use of DHEA supplementation to improve testosterone concentrations in elderly women. In addition, DHEA supplementation can also be used to decrease the BMI.

Conflict of interest

The authors have no conflict of interest to disclose.

Conflict of interest: The authors declare no conflict of interest

Funding: No funding was received for this study.

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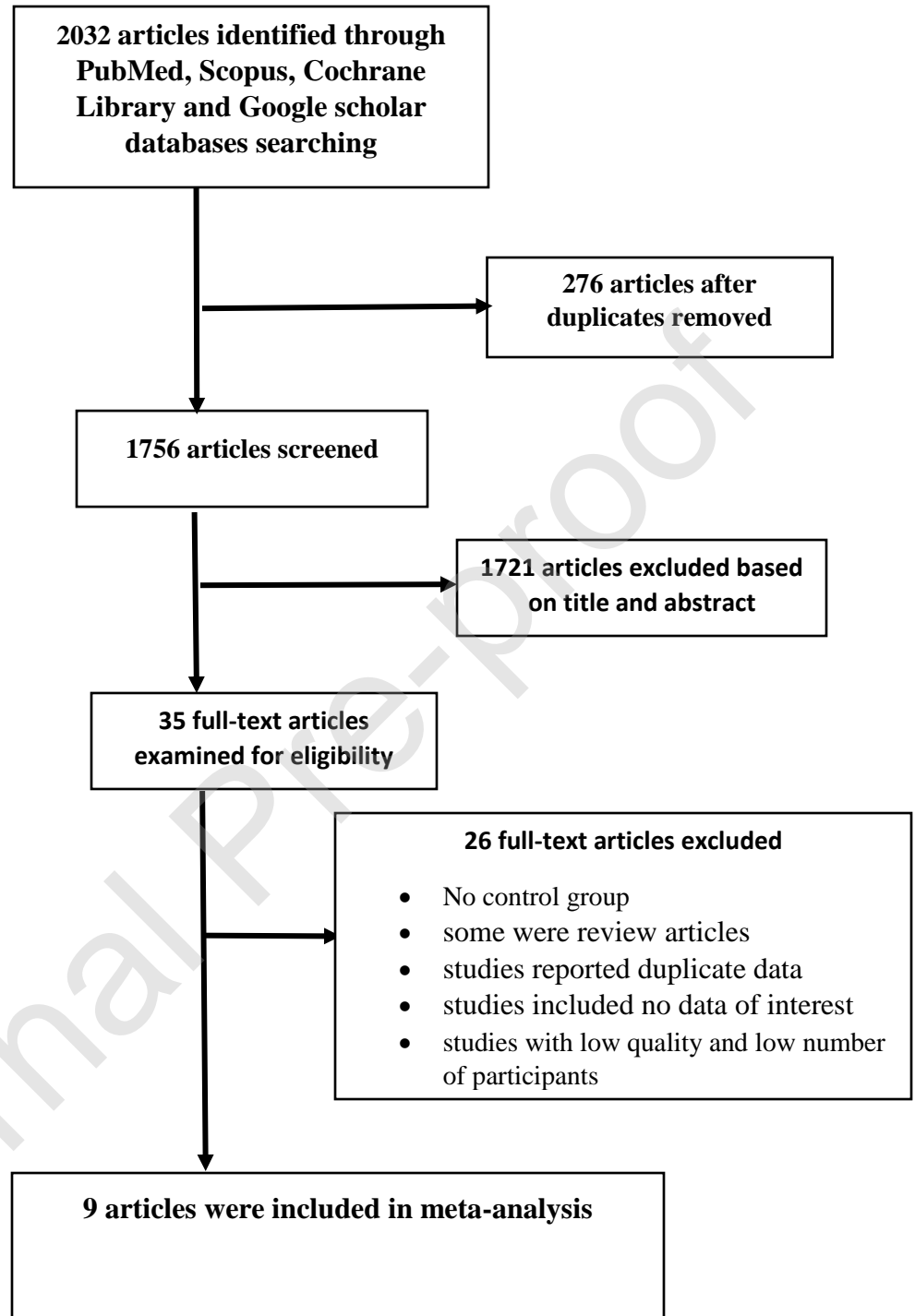


figure1. Flow chart for study examined and included into the meta-analysis.

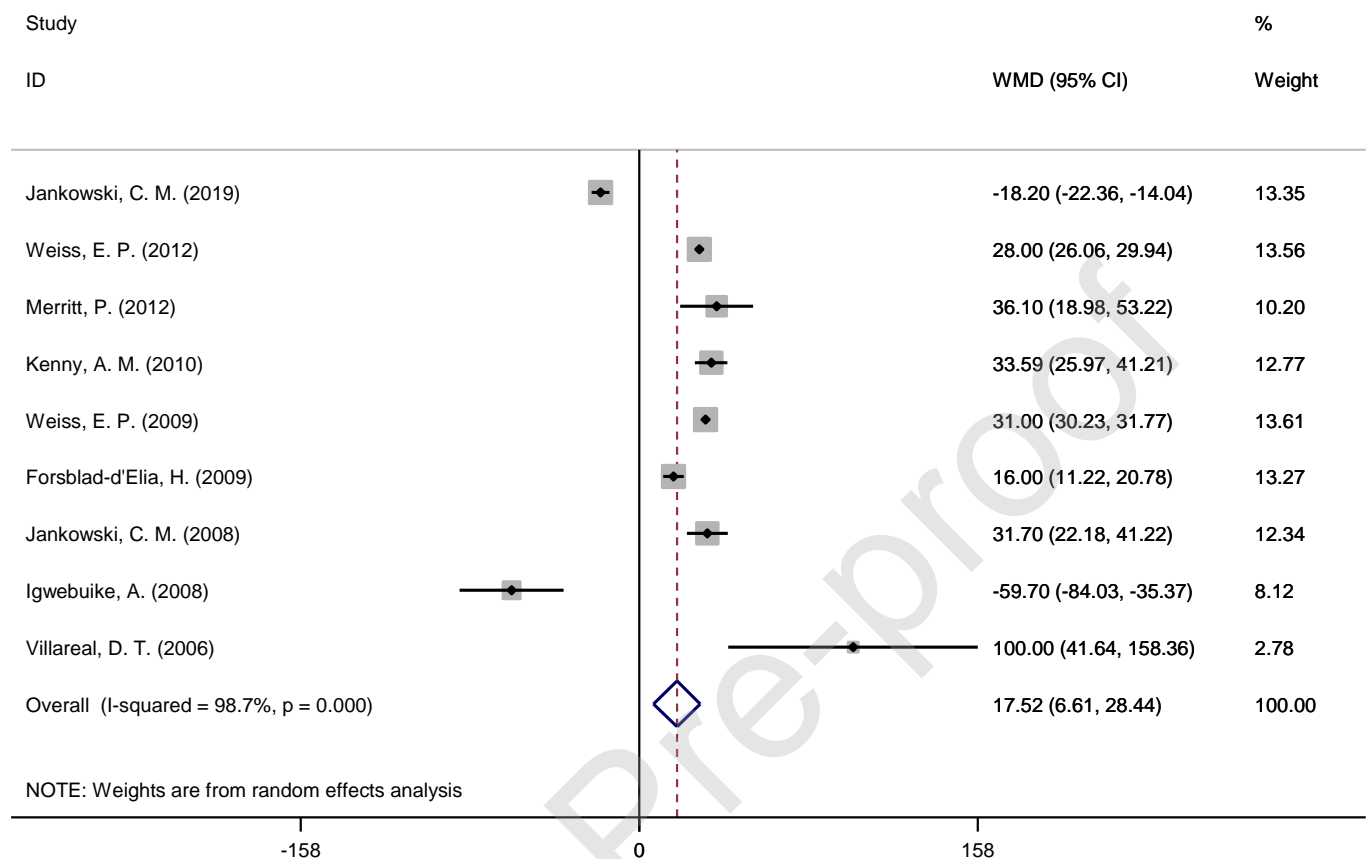


Figure2. Forest plot of randomized controlled trials investigating the effects of DHEA supplementation on testosterone level in elderly women. (Arrows: 95% Confidence Interval (CI) that exceed the limits of the graph, and the horizontal lines their 95% confidence intervals, squares: the weight of studies in meta-analysis, the horizontal tips represent the 95% CI, WMD: weighted mean difference, and diamond shapes: the center of the diamond represents the combined treatment effect).

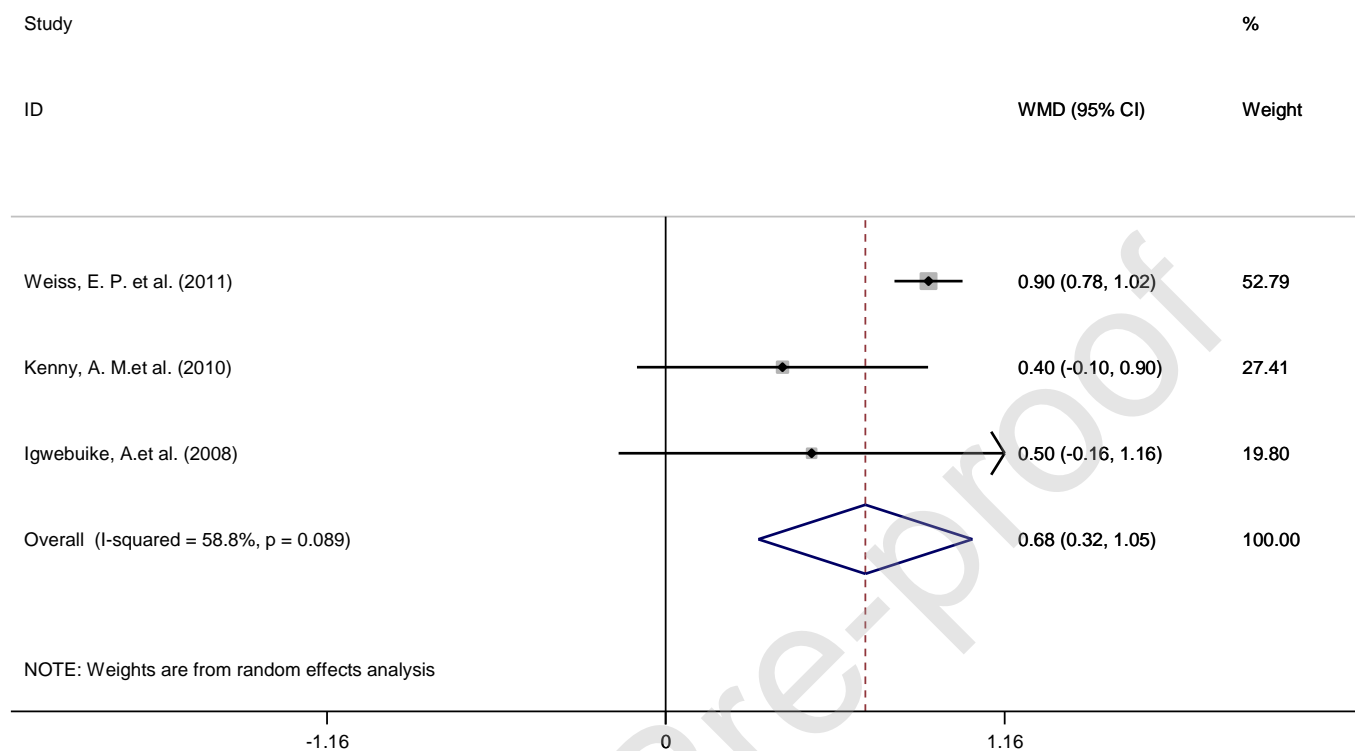
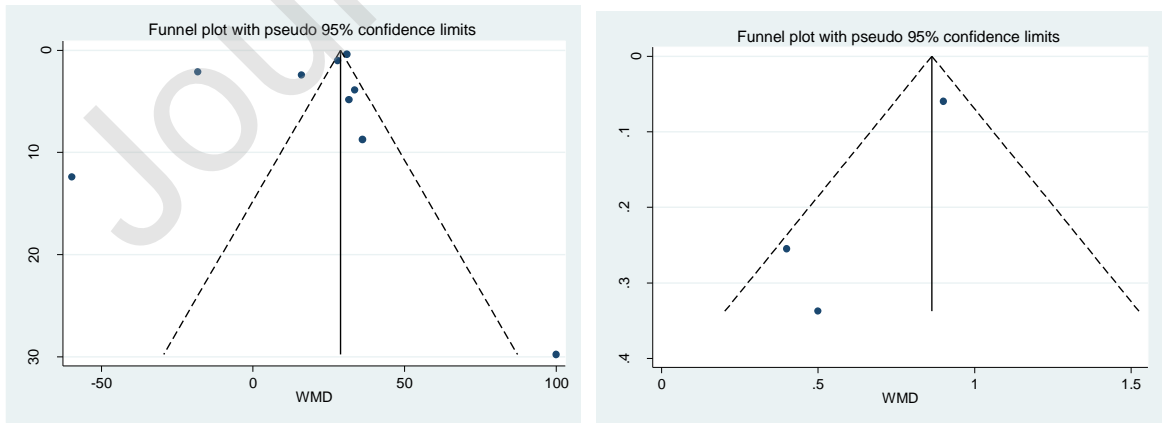


Figure3. Forest plot of randomized controlled trials investigating the effects of DHEA supplementation on LBM in elderly women



A) Testosterone (Coef.= 31.73; 95% CI : 22.87, 40.58; P= 0.251) B) LBM (Coef.= -1.95; 95% CI : -9.35, 5.44; P= 0.184)

Figure 4. Funnel plot of the weighted mean difference (WMD) versus the s.e. of the weighted mean difference (WMD).

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Table 1. Characteristics of eligible studies.

Author(year)	Cou ntry	Particip ants age(year)	Sample size DHEA /Placebo	Duration(weeks)	DHE A dosag e(mg/ d)
Jankowski, C. M. et al(2019)	USA	69	135/145	52	50
Weiss, E. P. et al (2011)	Italy	70	40/22	52	50
Merritt, P. et al (2012)	USA	63.5	24/48	4	50
Kenny, A. M. et al (2010)	USA	76.59	43/44	26	50
Weiss, E. P. et al (2009)	Italy	70	58/58	56	50
Forsblad-d'Elia, H. et al (2009)	Swe den	60.7	23/23	36	50
Jankowski, C. M. et al (2008)	USA	69	25/33	52	50
Igwebuike, A. et al (2008)	USA	64.59	17/17	12	50
Villareal, D. T. et al (2006)	USA	72	29/27	41	50

Section/topic	#	Checklist item	Rep on p
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1