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A dose-response and meta-analysis of dehydroepiandrosterone (DHEA) supplementation on testosterone levels: perinatal prediction of randomized clinical trials

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Abstract

Background: Dehydroepiandrosterone (DHEA) has been aggressively sold as a dietary supplement to boost testosterone levels although the impact of DHEA supplementation on testosterone levels has not been fully established. Therefore, we performed a systematic review and meta-analysis of RCTs to investigate the effect of oral DHEA supplementation on testosterone levels.

Methods: A systematic literature search was performed in Scopus, Embase, Web of Science, and PubMed databases up to February 2020 for RCTs that investigated the effect of DHEA supplementation on testosterone levels. The estimated effect of the data was calculated using the weighted mean difference (WMD). Subgroup analysis was performed to identify the source of heterogeneity among studies.

Results: Overall results from 42 publications (comprising 55 arms) demonstrated that testosterone level was significantly increased after DHEA administration (WMD: 28.02 ng/dl, 95% CI: 21.44-34.60, p=0.00). Subgroup analyses revealed that DHEA increased testosterone level in all subgroups, but the magnitude of increment was higher in females compared to men (WMD: 30.98 ng/dl vs. 21.36 ng/dl); DHEA dosage of >50 mg/d compared to ≤50 mg/d (WMD: 57.96 ng/dl vs. 19.43 ng/dl); intervention duration of ≤12 weeks compared to >12 weeks (WMD: 44.64 ng/dl vs. 19 ng/dl); healthy participants compared to postmenopausal women, pregnant women, non-healthy participants and androgen-deficient patients (WMD: 52.17 ng/dl vs. 25.04 ng/dl, 16.44 ng/dl and 16.47 ng/dl); and participants below 60 years old compared to above 60 years old (WMD: 31.42 ng/dl vs. 23.93 ng/dl).

Conclusion: DHEA supplementation is effective for increasing testosterone levels, although the magnitude varies among different subgroups. More study needed on pregnant women and miscarriage.

Keywords: DHEA; testosterone; pregnancy, women, meta-analysis

Introduction

In humans, dehydroepiandrosterone (DHEA) is a steroid hormone that is produced mainly in the zona reticularis of the adrenal gland, apart from the testes and ovaries (Acacio and others 2004; Collomp and others 2018). It is also a neuro-steroid that is formed *de novo* in the brain (Strous and others 2006). DHEA can be subsequently converted to its sulfated conjugate (DHEA-S) (Buster and Casson 2000); whereby both forms represent the most abundant steroid hormone in both sexes (Hornsby 1995). Although the *bona fide* hormone receptors, specific target tissues and exact mechanisms of action for DHEA remains unclear (Ebeling and Koivisto 1994), DHEA is known to possess weak androgenic activity (Barnhart and others 1999) in addition to being a pro-hormone precursor that is converted to testosterone, a highly potent androgen in men; and estrogen in women (Labrie and others 1997; Longcope 1996).

In humans, serum DHEA levels have been linked to bone and muscle health, feelings of well-being, improvements in concentration, cognition, improve in pregnancy rat, verbal and long-term memory, lower miscarriage rates, as well as increases in vigor and libido (Barrett-Connor and Edelstein 1994; Berr and others 1996; Gleicher and others 2009; Mortola and Yen 1990; Rudman and others 1990; Wolkowitz and others 1995; Yen and others 1995). On the contrary, low concentrations of DHEA have been associated with functional limitation, anxiety disorders during pregnancy, depressed symptomatology, poor subjective perceptions of health and life

satisfaction, and poor cognition (Berkman and others 1993; Leff-Gelman and others 2020; Sunderland and others 1989). Although DHEA plays such an important role in our overall health and well-being, its levels in our circulation actually decline steadily with age. Adrenal production of DHEA begins during puberty and peaks at around 20 years old. At approximately age 25, serum DHEA begins to decline rapidly, so that by age 75 DHEA level is ~80% lower than at 20 years old (Orentreich and others 1984; Orentreich and others 1992). As such, DHEA has been made available as a form of "over-the-counter" nonprescription oral dietary supplement.

Oral DHEA supplement has been suggested to be consumed by aging individuals to improve physical, mental and sexual health. Since DHEA is a precursor to testosterone, consumption of DHEA is naturally expected to increase the testosterone levels, which also wane with age in both sexes. As a hormone, testosterone is important for muscle mass, bone strength, hair growth, and sexual function in men. Symptoms of low testosterone levels include low energy, poor concentration, depression, low libido, and erectile dysfunction. Testosterone deficiency affects approximately 7% of men in their 50s, and increases with age (Halpern and Brannigan 2019). Due to its ready availability over the counter and its potential to alleviate testosterone deficiency, it is thus essential to establish if the link exists between oral DHA supplementation and the levels of testosterone. As of now, there have been numerous studies that investigated the effects of DHEA consumption with testosterone levels as one of the outcomes. In this work, we aimed to attain a more concrete relationship between DHEA supplementation and testosterone levels by integrating data from all randomized controlled trials (RCTs) on this aspect through a systematic review and meta-analysis.

Methods

This systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Guyatt and others 2008; McInnes and others 2018).

Search strategy

Four electronic databases (Scopus, Embase, Web of Science, and PubMed) were searched on 20 February 2020 for related publications. The following search terms were used: ("Dehydroepiandrosterone" OR DHEA OR Prasterone OR DHEAS) AND "clinical trials " OR "double-blind method OR "cross-over studies" OR "single-blind method" OR RCT OR "random allocation" OR "intervention studies" OR "controlled trial" OR "intervention" OR "randomized" OR "randomised" OR "randomly" "random" OR "assignment" OR "placebo". In addition, the reference lists of relevant studies were reviewed to discover potentially qualified publications.

Eligibility criteria

Two investigators independently screened the titles and abstracts of the retrieved publications. Full-text appraisal was subsequently executed. Disagreements were resolved by discussion between investigators. To be eligible, RCTs had to meet the following criteria:
(1) Population: adult subjects aged 18 to 80 years; (2) Intervention: DHEA supplementation at any dose; (3) Comparison: placebo group with head-to-head comparison; (4) Primary outcomes: publications that reported mean and SD of testosterone on baseline and final study. The most recent publications were used in case of duplication. The following types of studies were

excluded: (1) non-English publications; (2) non-randomized controlled trials; (3) letters; (4) publications containing insufficient data; and (5) animal studies.

Data extraction

Two investigators extracted the data independently using a standard excel sheet. The information extracted from each trial included the following: publication year, the first author, mean and SD of testosterone levels, intervention versus comparison, doses for DHEA, treatment period (week). We also communicated with the corresponding authors to obtained relevant data, if necessary.

Quality assessment

The risk of bias in the qualified publications was assessed using the Cochrane Collaboration's tool for risk of bias evaluations in RCTs. (Higgins and others 2011). This assessment tool considered the following domains: generation of the allocation sequence, allocation concealment, blinding of participants, masking of outcome assessors, blinding of results assessment, incomplete follow-up, selective reporting, and other potential sources of bias. The trials were categorized as high risk, low risk, and unclear risk of bias based on the mentioned domains. Publications with more than one key criterion was considered as possessing a high risk of bias, those without all domains were regarded as possessing a low risk of bias. Otherwise, they were reported as having an unclear risk of bias.

Statistical methods

Data was combined using the generic inverse variance method, with random effects model (DerSimonian-Laird approach), and described as weighted mean differences (WMDs) with 95% confidence intervals (CIs). We applied standard calculations to obtain the mean and SD when the data was stated in a different format (Higgins 2011; Hozo and others 2005). For example, when the SD of the modification was not stated in the publications, we derived it using the following formula: SD differences =square root [($SD_{baseline}^2$+SD_{end}^2) - (2×R× $SD_{baseline}$× SD_{end})]. Heterogeneity across comparisons was assessed by the Cochran Q and the I^2 tests. We explored the sources of heterogeneity by sensitivity analyses (in which each study was omitted individually and the combined effect size re-estimated) and subgroups analyses. Publication bias was discovered by means of Egger's and Begg tests and visual appraisal of funnel plots (Egger and others 1997). We used Stata program (Stata Corp. College Station, Texas, USA) for all analyses.

Results

Study selection

The initial database search yielded 5,024 records; following elimination of duplicates, 3,253 publications remained. In the next step, the abstracts and titles for all articles were screened, resulting in 87 papers for full-manuscript examination. Ultimately, 42 publications with 55 comparisons were included in this study (**Figure 1**) (Acacio and others 2004; Assies and others 2003; Barnhart and others 1999; Bloch and others 2012; Bloch and others 2013; Carranza-Lira and others 2002; Casson and others 1998; Christiansen and others 2011; Collomp and others 2018; Dhatariya and others 2005; Espinosa De Ycaza and others 2016; Forsblad-d'Elia and others 2009; Genazzani and others 2011; Gurnell and others 2008; Igwebuike and others 2008;

Jankowski and others 2019; Jedrzejuk and others 2003; Johannsson and others 2002; Kawano and others 2003; Kenny and others 2010; Kohut and others 2003; Lasco and others 2001; Malik and others 2015; Martina and others 2006; Morales and others 2009; Morales and others 1998; Nordmark and others 2005; Ostojic and others 2010; Panjari and others 2009; Poretsky and others 2006; Poretsky and others 2009; Schmidt and others 2005; Son and others 2020; Stanczyk and others 2009; Strous and others 2007; Villareal and Holloszy 2004; Villareal and Holloszy 2006; Weiss and others 2009; Weiss and others 2012; Williams and others 2004; Yamada and others 2010; Yuan and others 2016).

Characteristics of the eligible trials

The characteristics of the eligible trials are detailed in **Table 1**. Included papers were published between 1995 and 2019, and were conducted in different countries; including the USA, China, India, Israel, Italy, Denmark, Japan, France, Iran, Australia, Canada, Sweden, New Zealand, Germany, Poland, Netherlands, Mexico. The treatment duration varied between 3 weeks and 2-years, whilst daily administrated dosage of DHEA ranged from 25 to 270 mg. Studies were conducted on both genders, whereby the number of participants ranged from 9 to 281, whilst the study population consisted of postmenopausal women, healthy individuals, non-healthy individuals (patients undergoing IVF-ET, infertile women with POA, women suffering from anorexia nervosa, mild to moderate cognitive impairment, patients with HIV infection, schizophrenia patients, patients with systemic lupus erythematosus, men with hypercholesterolemia, patients with X-linked adrenoleukodystrophy), and androgen-deficient patients. Risk of bias and methodological quality of eligible trials are described in **Supplemental Table 1.**

Meta-analysis results

Impact of DHEA administration on testosterone

55 arms, with 2,880 subjects (case=1,422, and control=1,458), described testosterone as an outcome measure. Overall results demonstrated that testosterone level was significantly increased after DHEA administration (WMD: 28.02 ng/dl, 95% CI: 21.44, 34.60, p =0.00), with significant heterogeneity across the trials (I^2 =97%, p =0.000) (**Figure 2**).

Subgroup analysis

We subsequently stratified our analysis based on gender, DHEA dosage, intervention duration, health status of participants and age. Significant association was observed in all subgroups, but at different magnitudes. For the gender subgroup, a higher level of testosterone increment were found in women (WMD: 30.98 ng/dl, 95% CI: 23.42, 38.54, I^2=98%) compared to the men (WMD: 21.36 ng/dl, 95% CI: 3.64, 39.08, I^2=81%) **(Table 2)**. Subgroup analyses based on DHEA dosage revealed that studies with >50 mg/d of DHEA supplement showed a higher testosterone level increment (WMD: 57.96 ng/dl, 95% CI: 29.87, 86.06, I2=97%) compared to studies with ≤50 mg/d (WMD: 19.43 ng/dl, 95% CI: 12.47, 26.40, I^2=98%). Across the treatment durations, subgroup of participants receiving ≤12 weeks intervention showed a higher increment in testosterone levels (WMD: 44.64 ng/dl, 95% CI: 31.58, 57.70, I^2 =98 %) compared to participants undergoing >12 weeks of intervention (WMD: 19 ng/dl, 95% CI: 11.78, 26.22, I^2=96%). DHEA also increased testosterone level at a higher magnitude in healthy participants (WMD: 52.17 ng/dl, 95% CI: 11.12, 93.23, I2=95%) as compared to postmenopausal women (WMD: 25.04 ng/dl, 95% CI: 15.76, 34.32, I2=98%), non-healthy participants (WMD: 16.44

ng/dl, 95% CI: 2.09, 30.80, I2=90%) and androgen-deficient patients (WMD: 16.47 ng/dl, 95% CI: 3.99, 28.95, I2=93%). Moreover, the increment in testosterone level was also higher among participants below 60 years old (WMD: 31.42 ng/dl, 95% CI: 22.22, 40.62, I2=97%) when compared to participants who were above 60 years old (WMD: 23.93 ng/dl, 95% CI: 15.35, 32.52, I2=97%) (**Table 2).**

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

Figure 4 depicts the results of the non-linear dose-response meta-analysis. The results showed that DHEA significantly increased testosterone for DHEA dosages up to 100 mg/day (p=0.034) (**Figure 3)**.

Sensitivity analysis

To ascertain the influence of each single trial on the meta-analyses, we excluded each arm from the overall effect size, step by step. No significant impact of any individual study was observed on the overall effect sizes.

Publication bias

Visual inspection of funnel plot established no evidence of publication bias in the present study (**Figure 4**). Egger's (p=0.807) and Begg (p=0.396) tests also confirmed the funnel plot conclusion.

Discussion

DHEA and DHEA-S are the most abundant steroid hormones in humans, whereby their best-known function is to act as a precursor for sex hormone biosynthesis. Hence, it has been proposed that DHEA mediates its effects predominantly via its metabolites (Johannsson and others 2002). DHEA-S conjugates are formed in the adrenal cortex as a result of sulfation of DHEA by sulfuryl transferase (Giagulli and others 1993; Giagulli and others 1989). DHEA-S itself does not harbor much potency, but instead may represent a reservoir pool for DHEA. This pool can be readily converted back to DHEA by steroid sulfatases in peripheral target tissues for the synthesis of androgens and estrogens (Hobkirk 1985; Labrie and others 2005). The biosynthesis of sex hormones in the target tissues first involves the transformation of DHEA to androstenedione, which is then converted to testosterone and to dihydrotestosterone (DHT), the two most potent androgens. Similarly, androstenedione is converted to the weak estrogen, estrone, which is subsequently converted to the most potent estrogen, 17A-estradiol in women. Besides, to a lesser extent testosterone also contributes to the formation of 17A-estradiol (Sokol and others 1982; Stanczyk and others 2009).

Despite the fact that a large proportion of the biochemical effects of DHEA and DHEA-S comes from their metabolites, they have also been demonstrated to play direct roles as hormones, albeit a specific nuclear receptor has yet to be conclusively determined in humans. Existing literature shows that DHEA can participate directly in a number of biochemical pathways. First, DHEA has been demonstrated to not only increase eNOS activity but also enhance the levels of intracellular cyclic guanosine monophosphate (cGMP) when endothelial cells were exposed to varying concentrations of DHEA. This implies that DHEA is directly involved the NOS/cGMP

signaling pathway (Liu and Dillon 2002; Liu and Dillon 2004; Simoncini and others 2003). Another pathway that has been implicated is the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway whereby DHEA is known to activate NF-kB (Radford and others 2010). Besides, Radford et al. also reported the direct activation of protein kinase C beta (PKC-b) by DHEA-S, and in the same study PKC-b was proposed as an intracellular receptor for DHEA-S in human neutrophils (Radford and others 2010). In addition, other derivatives of DHEA such as the 7a and 7b-hydroxylated derivatives have been reported to be involved actively in physiology via a number of putative nuclear receptors (Davidson and others 2008; Hennebert and others 2008; Le Mée and others 2008; Niro and others 2010). As a result, the modulatory effects of DHEA and DHEA-S on human physiology is much wider than previously thought, encompassing endothelial function, cellular immunity and the inflammation process. They have been linked to a variety of health-related conditions of the cardiovascular system, body composition, bone metabolism and skin; apart from sexual function, neuroprotection, frailty and mortality as comprehensively discussed by Traish et al. (Traish and others 2011).

In this systematic review and meta-analysis, we focused on the effects of DHEA supplement on the levels of plasma testosterone, which can be considered an important metabolite of DHEA thanks to its conversion into testosterone in different tissues (Labrie and others 1997; Morales and others 1994). In men, testosterone is necessary for sexual function and libido (Buvat and others 2010). Besides, it also plays an important role in the development of the penis and testes, the deepening of the voice during puberty, sperm production, appearance of facial and pubic hair, in balding, bone growth, muscle size and strength. Though touted as a male hormone, women too, require a minimum level of testosterone for their sexual response, besides ovarian

function and bone strength (Davis and others 2005). However, both DHEA and DHEA-S decline in a drastic, age-related fashion in both genders (Casson and Buster 1995). Whereas, the levels of plasma testosterone remain relatively stable in women even after menopause, whilst circulating testosterone tends to decline slowly in ageing men. The declines of DHEA and DHEA-S are often accompanied by various age-related disorders, including deterioration in libido and sexual function; increased risk of cardiovascular events; malignancy; and osteoporosis (Barrett-Connor and others 1986; Ebeling and Koivisto 1994; Sambrook and others 1992). Thus, DHEA(S) has been regarded as a putative biomarker for aging, and restoring them to their youthful levels with external supplementation has been speculated to retard the aging process (Orentreich and others 1984).

It is noteworthy that DHEA has been classified as a dietary supplement and made widely available over the counter in the United States since 1994, despite the fact that the metabolic fate of orally ingested DHEA remains not elucidated. It is believed that orally ingested DHEA may be converted to androgens or estrogens, similar to its natural counterpart (Kohut and others 2003). Notwithstanding, it has been postulated that DHEA therapy is safer than estrogen and testosterone because it and its sulfate (DHEAS) first circulate as an inactive prohormone that can be converted into active ones by means of specific enzymatic pathways present at target tissue levels (Giagulli and others 1993; Giagulli and others 1989). Although the therapeutic uses for DHEA have been extensively discussed in various reviews and editorials (Eskandari and Cizza 2002), many of these claims have been derived from rodent data, which cannot be directly translated to the human physiology (Baulieu 1996). It is therefore important to measure the circulating levels of DHEA and its metabolites after DHEA administration not only to ascertain

the efficacy of oral DHEA supplement, but also to monitor any adverse effects caused by the overproduction of androgens or estrogens (Stanczyk and others 2009).

As for our finding from the overall meta-analysis, DHEA supplementation was found to increase plasma testosterone level. Meanwhile, in subgroup analysis, DHEA was found to increase testosterone level in all subgroups, but the magnitude of increment was higher in: (i) females; (ii) participants who received a higher dose (>50 mg/day) of DHEA, (iii) participants who took the supplement for less than 12 weeks; (iv) in healthy subjects (compared to postmenopausal women, participants with an underlying disorder, and participants who are androgen-deficient) and (v) younger participants (below 60 years old). The results from our overall analysis are hardly surprising because most of the eligible studies that were included in our meta-analysis pointed towards this direction despite the heterogeneity of the subject population. In fact, only five studies had reported no significant association (Casson and others 1998; Malik and others 2015; Morales and others 2009; Poretsky and others 2006; Villareal and Holloszy 2004). Furthermore, the transformation of DHEA to testosterone has been a well-established subject although the metabolic fate of orally ingested DHEA has not been fully elucidated. Nevertheless, how far can these statistically significant increases in testosterone levels be translated into physiologically or clinically meaningful benefits remains unclear. For example, the measured WMD values can be assay-dependent and therefore some statistically significant WMDs may lie within the limits of variation of a selected testosterone measurement method. These and other factors that can influence the validity of androgen assays have been comprehensively discussed by Carruthers et al. (Carruthers and others 2007).

In our subgroup analysis, female recipients of DHEA supplements were found to exhibit a higher magnitude of increment in their plasma testosterone. This observation is consistent with many studies. For example, the levels of plasma testosterone has been demonstrated to increase significantly upon DHEA supplementation for women suffering from hypoactive sexual desire disorder, middle-age and also older women; all relative to their male counterparts who demonstrated a small but significant positive effect (Corona and others 2013) or non-significant associations (Bloch and others 2013; Collomp and others 2018; Gurnell and others 2008) . In our case, our male subjects actually exhibited positive association although the magnitude of increase in plasma testosterone was smaller compared to the female subjects. The discrepancy between male and female subjects can be explained by the basal levels of testosterone levels inherent in each gender. In general, men have higher basal levels of testosterone, which are likely to have obscured the relatively small additional effect of the administered DHEA (Genazzani and others 2011; Srinivasan and others 2009).

On the other hand, it is higher conceivable that higher intake of DHEA supplement, i.e. >50 mg/day should theoretically lead to a higher magnitude of increase in testosterone levels, given that the biosynthetic pathways of testosterone is not disrupted in the subjects under study. However, it should be noted that higher dosages of DHEA intake may also lead to undesirable side effects as mentioned above. As to why healthy and young subjects tend to display a more significant increase in the levels of testosterone, we speculate that, relative to these individuals, older and unhealthy subjects are more likely to experience any forms of genetic or metabolic disorders; and supplying DHEA alone may not fully restore the activity of testosterone biosynthesis.

The primary strength of our study is that we have integrated data from a large number of meticulously selected RCTs (N=42, comprising 55 arms), thereby significantly improving the statistical power of analysis. Furthermore, these chosen studies had been conducted in 17 countries, so as to accommodate diversity in culture, lifestyle and genetic background. A limitation of this meta-analysis is that the RCTs included are heterogeneous, mainly in terms of sample sizes, mean ages (~20- to ~70 years old), and health statuses. Apart from that, we also noticed that a range of techniques have been used for measuring plasma testosterone levels, such as radio-immunoassays, chemiluminescence immunoassays and liquid chromatography – mass spectrometry which is the current method of choice. This is most probably due to the historical span of the included literature (1995-2019).

Conclusion

In summary, our systematic review and meta-analysis that was based on 42 RCTs revealed that oral administration of DHEA supplement was associated fully to the increase of plasma testosterone levels in both genders. However, the increase in plasma testosterone is more prominent among females, healthy and younger subjects and when DHEA supplement is consumed for >50mg/day for < 12 weeks.

Conflict of interest

There was no conflict of interest declared by the authors.

Authors' contributions to manuscript

HK and AH designed and conducted the research; SHT and VKH screened and extracted articles data; HK_V executed statistical analysis; TYL and SHT wrote the paper; AH had primary responsibility for final content. All authors read and approved the final manuscript.

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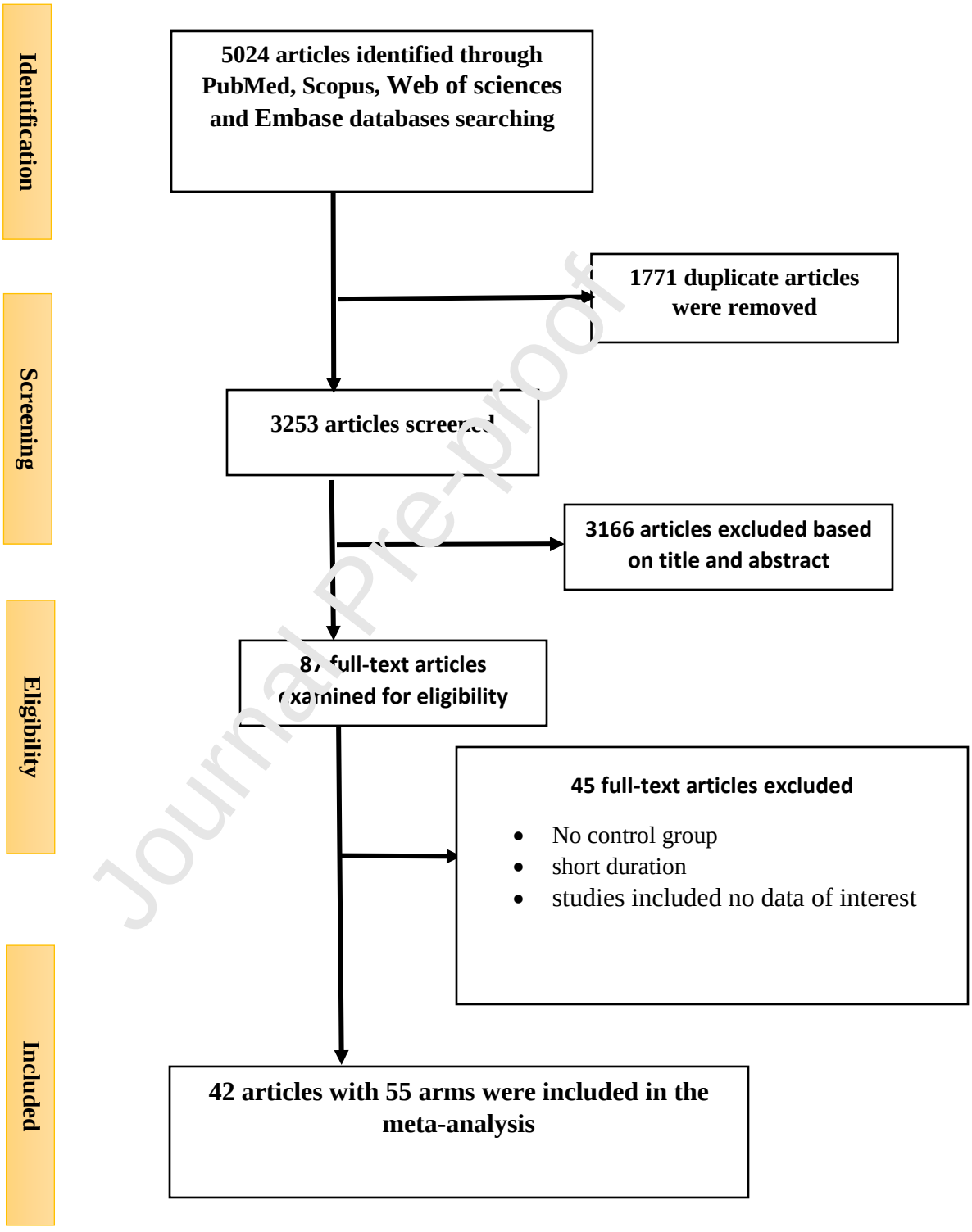


Figure1. Flow chart for studies examined and included into the meta-analysis.

Figure2. Forest plot of randomized controlled trials investigating the effects of DHEA supplementation on Testosterone

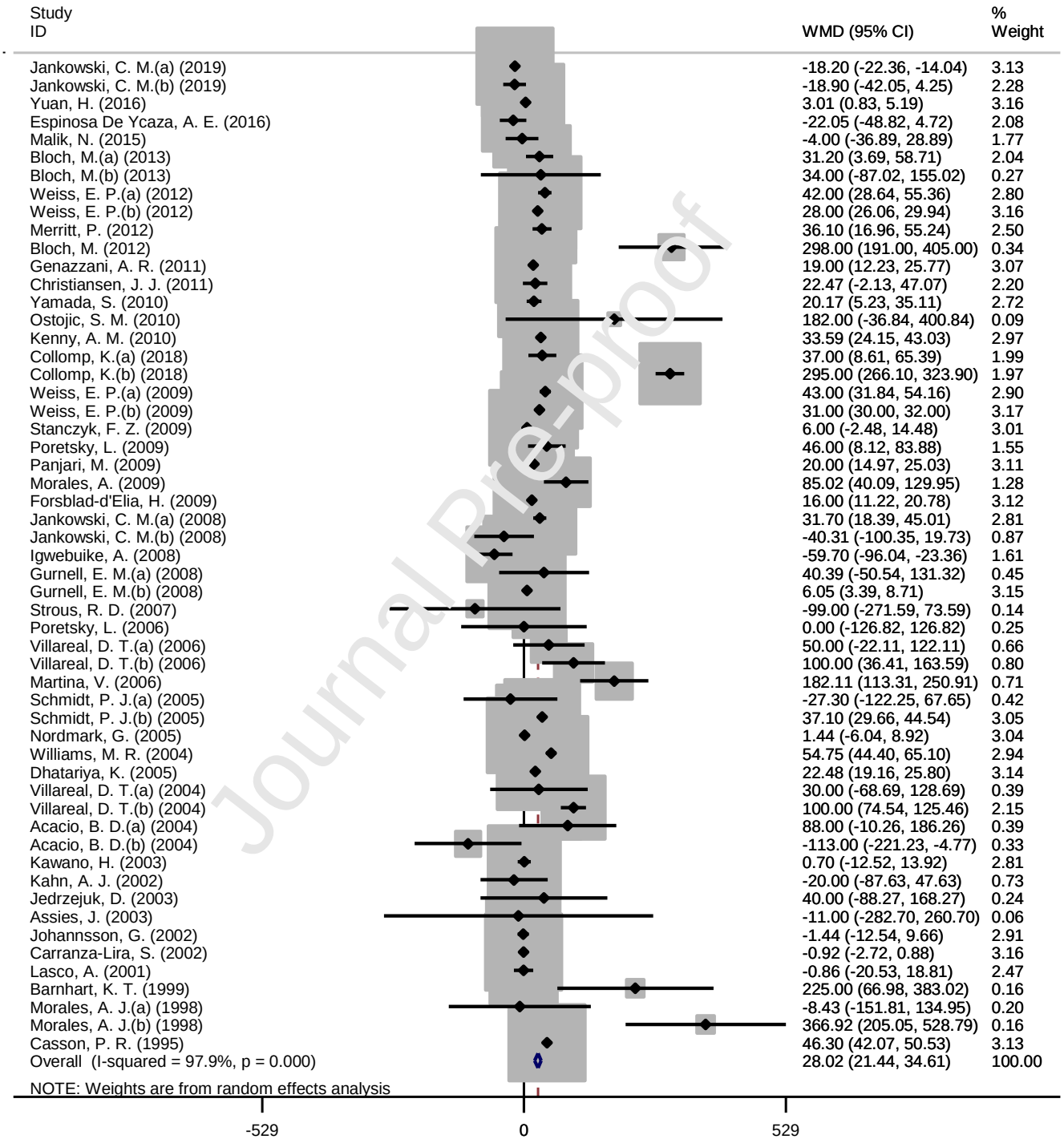
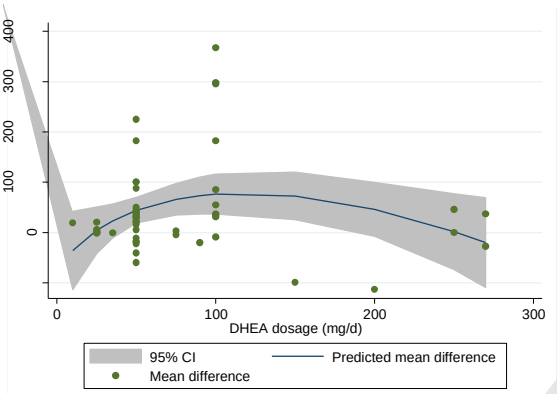


Figure 3. Non-linear dose-responses between DHEA and unstandardized mean difference in testosterone (ng/dl). The 95% CI is depicted in the shaded regions.

p= 0.034



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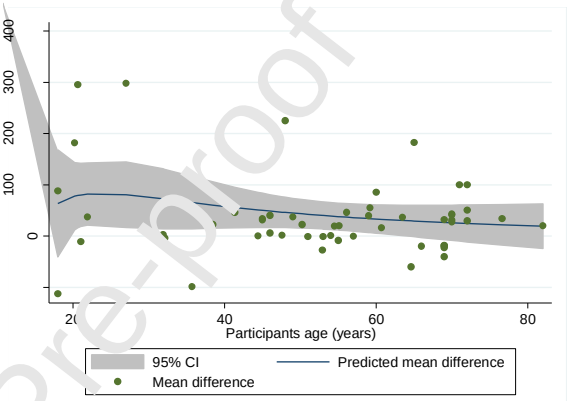

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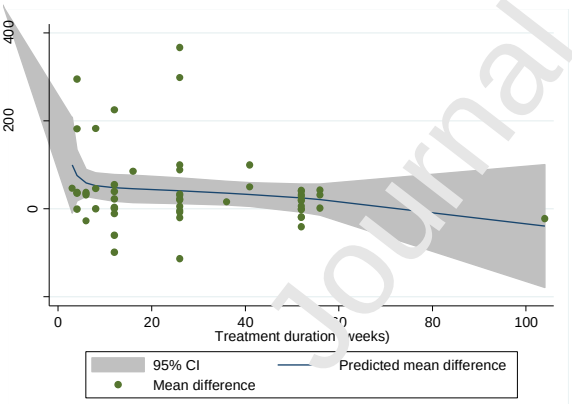
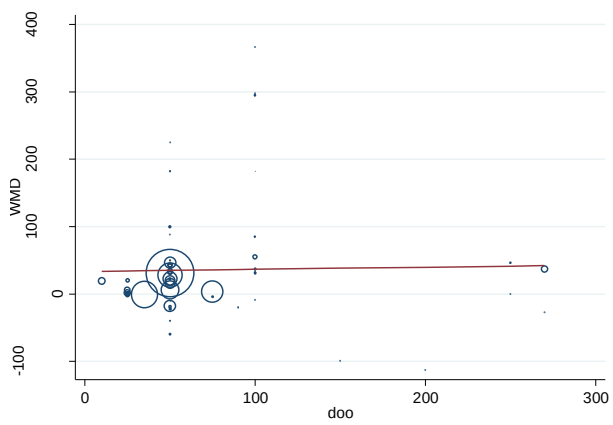
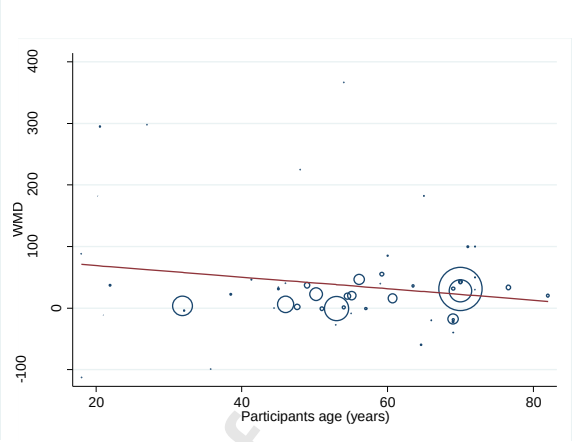


p= 0.857

p= 0.151

p= 0.073





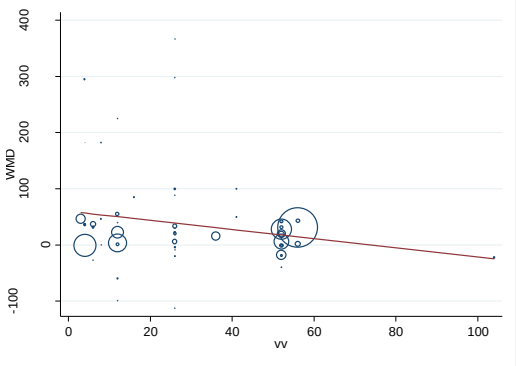


Figure 4. Funnel plot of the weighted mean difference (WMD) versus the s.e. of the weighted mean difference (WMD).

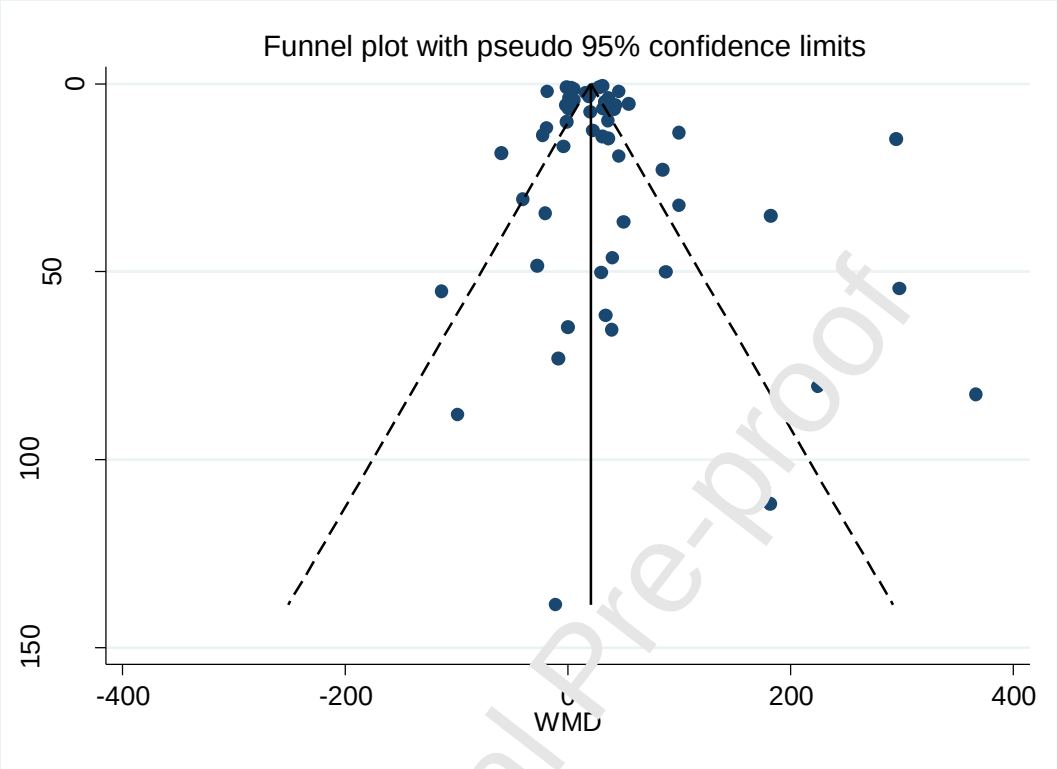


Table 1. Characteristics of eligible studies.

Author	year	Country	Population	Participents age(year)	Sex (f= female, m= male)	Sample size DHEA /Placebo	Duration(weeks)	DHEA dosage(mg/d)
Jankowski, C. M.(a)	2019	USA	older adults	69	[illegible]	135/145	12 months	50
Jankowski, C. M.(b)	2019	USA	older adults	69	[illegible]	143/138	12 months	50
Yuan, H.	2016	China	patients undergoing IVF-ET	31.85	f	98/95	3 month	75
Espinosa De Ycaza, A. E.	2016	USA	elderly men	69	m	29/29	2-years	50
Malik, N.	2015	India	infertile women with POA	32.1	f	25/25	6 months	75
Bloch, M.(a)	2013	Israel	Postmenopausal women	45	f	13/13	6 weeks	100
Bloch, M.(b)	2013	Israel	men	45	m	12/13	6 weeks	100
Weiss, E. P.(a)	2012	Italy	older adults	70	m	20/22	12 months	50
Weiss, E. P.(b)	2012	Italy	older adults	70	f	20/22	12 months	50
Merritt, P.	2012	USA	post-menopausal women	63.5	f	24/48	4 weeks	50
Bloch, M.	2012	Israel	women suffering from anorexia nervosa	27	f	13/8	6 months	100
Genazzani, A. R.	2011	Italy	postmenopau	54.5	f	12/12	12 months	10

			sal women					
Christiansen, J. J.	2011	Denmark	female patients with adrenal failure	38.5	f	10/10	6 months	50
Yamada, S.	2010	Japan	mild to moderate cognitive impairment	82	f	12/15	6 months	25
Ostojic, S. M.	2010	Iran	Young Athletes	20.2	m	10/10	28 days	100
Kenny, A. M.	2010	USA	Frail Older Women	76.55	f	43/44	6 months	50
Collomp, K.(a)	2018	France	healthy young	21.9	m	10/10	4 weeks	100
Collomp, K.(b)	2018	France	healthy young	20.6	f	11/11	4 weeks	100
Weiss, E. P.(a)	2009	Italy	older adults	70	m	55/55	13 months	50
Weiss, E. P.(b)	2009	Italy	older adults	70	f	58/58	13 months	50
Stanczyk, F. Z.	2009	USA	postmenopausal women	55 to 65	f	7/7	6 months	25
Poretsky, L.	2009	USA	Premenopausal Women with HIV Infection	41.33	f	9/6	8 weeks	250
Panjari, M.	2009	Australia	postmenopausal women	55.1	f	29/32	52 weeks	50
Morales, A.	2009	Canada	men	60	m	25/28	4 months	100
Forsblad-d'Elia, H.	2009	Sweden	with sexual dysfunction and androgen deficiency	60.7	f	23/23	9 months	50
Jankowski, C. M.(a)	2008	USA	postmenopau	69	f	25/33	12 months	50

			sal women with primary Sjogrens syndrome					
Jankowski, C. M.(b)	2008	USA	Older Adults	69	m	30/31	12 months	50
Igwebuike, A.	2008	USA	Older Adults	64.59	f	17/17	12 weeks	50
Gurnell, E. M.(a)	2008	New Zealand	Postmenopausal Women	46	m	24/24	12 months	50
Gurnell, E. M.(b)	2008	New Zealand	Primary Adrenal Insufficiency	46	f	30/32	12 months	50
Strous, R. D.	2007	Israel	Primary Adrenal Insufficiency	35.70000	both	20/20	12 weeks	150
Poretsky, L.	2006	USA	schizophrenia patients	44.4	m	31/38	8 weeks	250
Villareal, D. T.(a)	2006	USA	men with HIV infection	72	m	29/27	10 months	50
Villareal, D. T.(b)	2006	USA	elderly women and men	72	f	29/27	10 months	50
Martina, V.	2006	Italy	elderly women and men	65	m	12/12	2 months	50
Schmidt, P. J.(a)	2005	USA	elderly male subjects	52.9	m	23/23	6 weeks	270
Schmidt, P. J.(b)	2005	USA	Midlife-Onset Major and Minor Depression	49	f	23/23	6 weeks	270
Nordmark, G.	2005	Sweden	Midlife-Onset Major	47.6	f	20/17	13 months	25

			and Minor Depression					
Williams, M. R.	2004	Australia	female patients with systemic lupus erythematosus	59.2	f	18/18	3 months	100
Dhatariya, K.	2005	USA	healthy postmenopausal women	50.2	f	28/28	12 weeks	50
Villareal, D. T.(a)	2004	Germany	Hypoadrenal Women	72	m	15/14	6 months	50
Villareal, D. T.(b)	2004	Germany	Elderly Men	71	f	13/14	6 months	50
Acacio, B. D.(a)	2004	USA	Elderly Women	18	m	4/5	6 months	50
Acacio, B. D.(b)	2004	USA	healthy young men	18	m	5/5	6 months	200
Kawano, H.	2003	Japan	healthy young men	54	m	12/12	12weeks	25
Kahn, A. J.	2002	USA	men with hypercholesterolemia	66	m	43/43	6 months	90
Jedrzejuk, D.	2003	Poland	Elderly Men	59	m	12/12	3 months	50
Assies, J.	2003	Netherlands	healthy men	21	m	15/15	3 months	50
Johannsson, G.	2002	Sweden	patients with X-linked adrenoleucodystrophy	51	m	19/19	12 months	25
Carranza-Lira, S.	2002	Mexico	Hypopituitary Androgen-Deficient Women	53	f	10/10	1 months	35

Lasco, A.	2001	Italy	healthy postmenopausal women	57	f	10/10	12 months	25
Barnhart, K. T.	1999	USA	postmenopausal women	48	f	29/29	3 months	50
Morales, A. J.(a)	1998	USA	Perimenopausal Women	55	m	9/9	6 months	100
Morales, A. J.(b)	1998	USA	in age-advanced men	54	f	10/10	6 months	100
Casson, P. R.	1995	USA	in age-advanced women	56.1	[illegible]	11/11	3 Weeks	50

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

Subgrouped by	No. of trials	WMD	95% CI		P Value	P for heterogeneity	I^2 (%)	P for between subgroup heterogeneity
Age (years)								0.000
<60	33	31.426	22.227	40.626	0.000	0.000	97	
≥60	22	23.939	15.353	32.525	0.000	0.000	97	
Dosage								0.000
≤50mg	36	19.439	12.475	26.404	0.000	0.000	98	
>50mg	19	57.968	29.871	86.065	0.000	0.000	97	
Intervention duration (weeks)								0.000
≤12	23	44.642	31.583	57.701	0.000	0.874	98	
>12	32	19.003	11.783	26.223	0.000	0.025	96	
Gender								0.000
female	23	30.982	23.421	38.543	0.000	0.000	98	
male	31	21.363	3.646	39.081	0.018	0.000	81	
Healthy status								
Postmenopausal women	19	25.046	15.767	34.324	0.000	0.000	98	0.000
healthy	18	52.179	11.121	93.236	0.013	0.000	95	
non-healthy	12	16.449	2.094	30.805	0.025	0.000	90	
Androgen-Deficient	6	16.474	3.997	28.950	0.010	0.000	93	

Highlighted

1- DHEA administration was associated with increase in testosterone level.

2- DHEA increased testosterone level in all subgroups, but the magnitude of increment was higher in females compared to men; DHEA dosage of >50 mg/d compared to ≤50 mg/d; intervention duration of ≤12 weeks compared to >12 weeks;

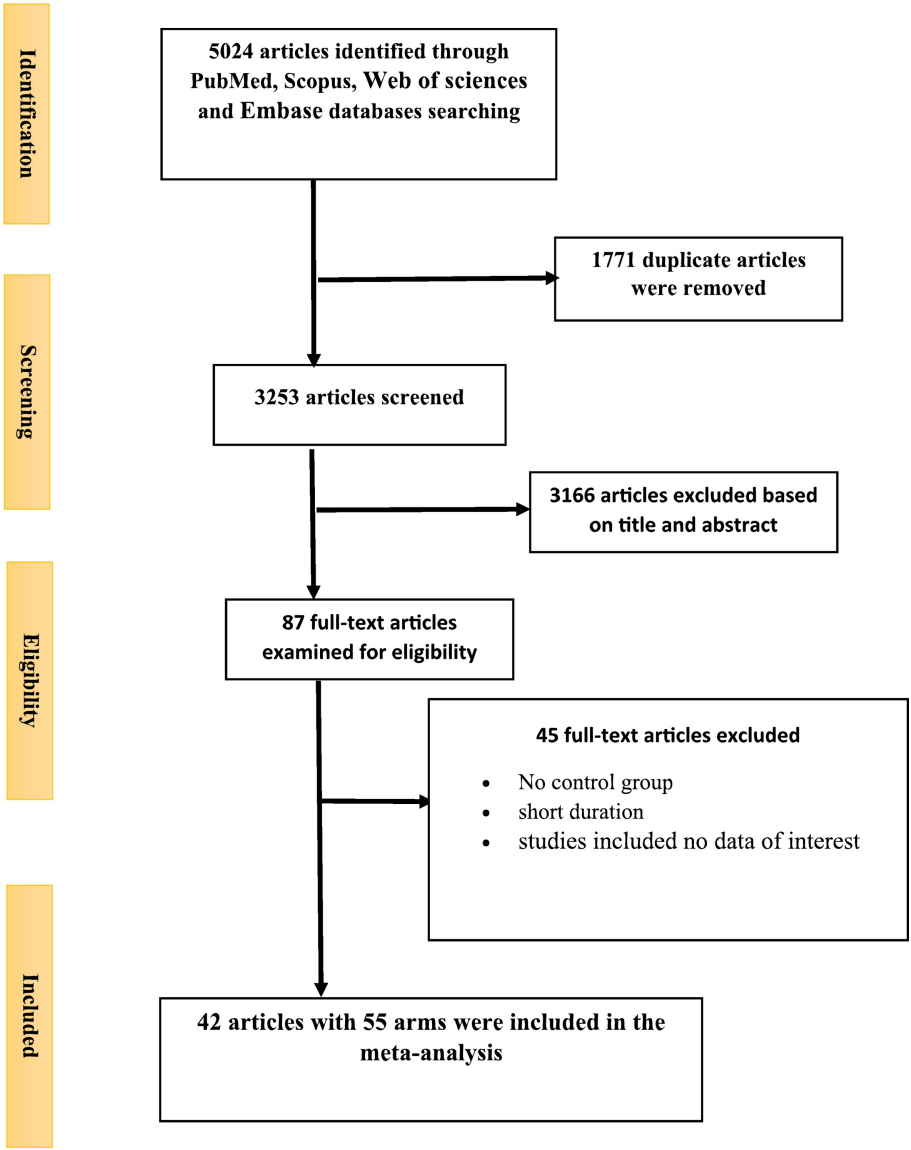

Identification
Screening
Eligibility
Included
5024 articles identified through PubMed, Scopus, Web of sciences and Embase databases searching
1771 duplicate articles were removed
3253 articles screened
3166 articles excluded based on title and abstract
87 full-text articles examined for eligibility
45 full-text articles excluded
No control group
short duration
studies included no data of interest
42 articles with 55 arms were included in the meta-analysis

Figure 1

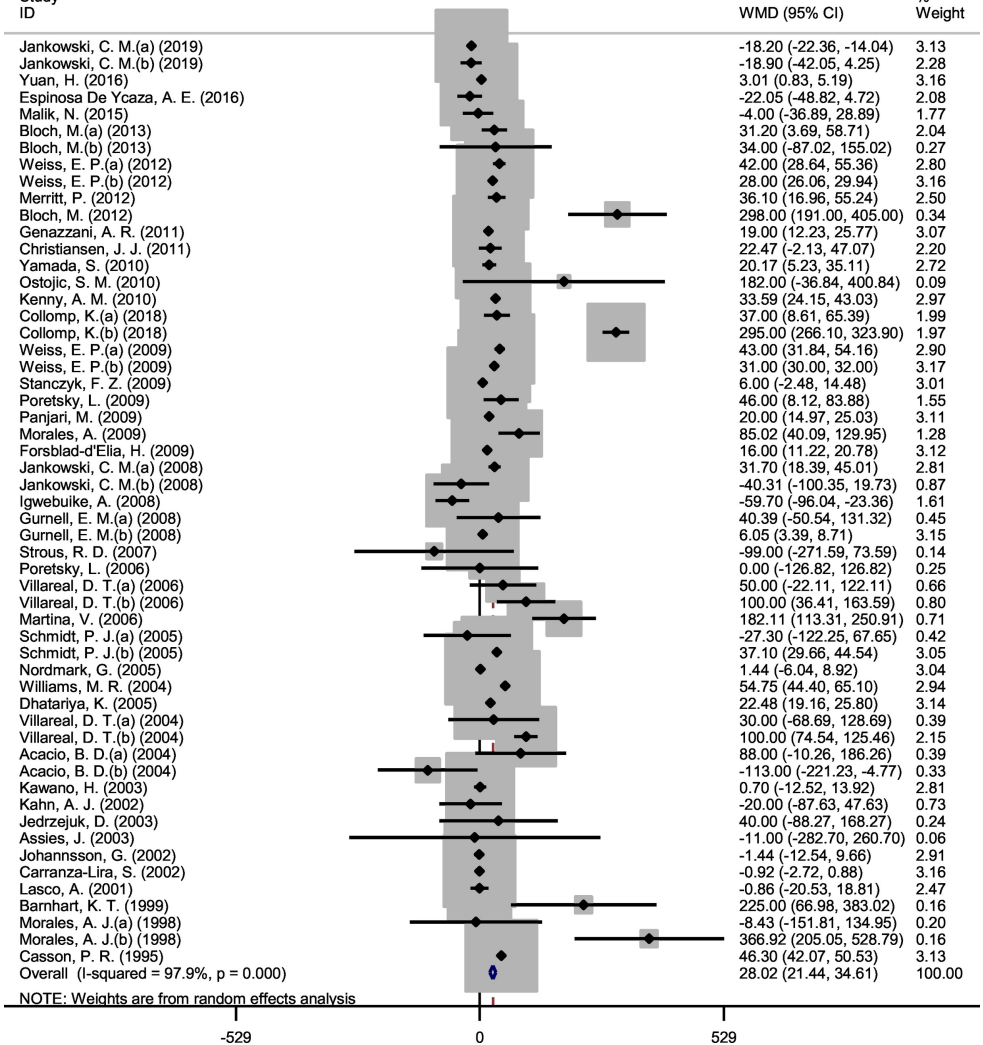
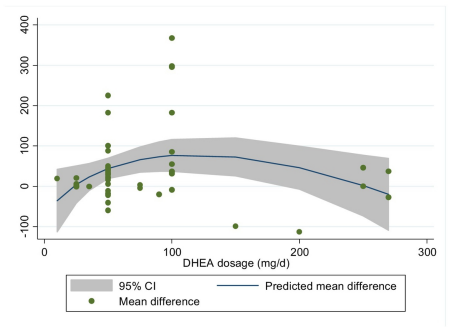
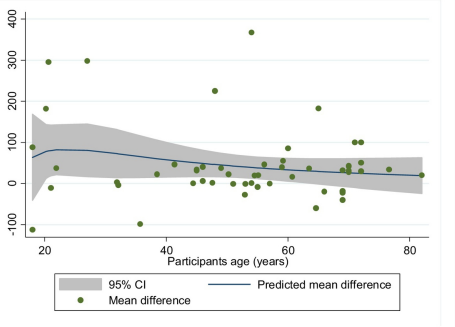

Study ID
WMD (95% CI)
% Weight
Jankowski, C. M.(a) (2019) -18.20 (-22.36, -14.04) 3.13
Jankowski, C. M.(b) (2019) -18.90 (-42.05, 4.25) 2.28
Yuan, H. (2016) 3.01 (0.83, 5.19) 3.16
Espinosa De Ycaza, A. E. (2016) -22.05 (-48.82, 4.72) 2.08
Malik, N. (2015) -4.00 (-36.89, 28.89) 1.77
Bloch, M.(a) (2013) 31.20 (3.69, 58.71) 2.04
Bloch, M.(b) (2013) 34.00 (-87.02, 155.02) 0.27
Weiss, E. P.(a) (2012) 42.00 (28.64, 55.36) 2.80
Weiss, E. P.(b) (2012) 28.00 (26.06, 29.94) 3.16
Merritt, P. (2012) 36.10 (16.96, 55.24) 2.50
Bloch, M. (2012) 298.00 (191.00, 405.00) 0.34
Genazzani, A. R. (2011) 19.00 (12.23, 25.77) 3.07
Christiansen, J. J. (2011) 22.47 (-2.13, 47.07) 2.20
Yamada, S. (2010) 20.17 (5.23, 35.11) 2.72
Ostojic, S. M. (2010) 182.00 (-36.84, 400.84) 0.09
Kenny, A. M. (2010) 33.59 (24.15, 43.03) 2.97
Collomp, K.(a) (2018) 37.00 (8.61, 65.39) 1.99
Collomp, K.(b) (2018) 295.00 (266.10, 323.90) 1.97
Weiss, E. P.(a) (2009) 43.00 (31.84, 54.16) 2.90
Weiss, E. P.(b) (2009) 31.00 (30.00, 32.00) 3.17
Stanczyk, F. Z. (2009) 6.00 (-2.48, 14.48) 3.01
Poretsky, L. (2009) 46.00 (8.12, 83.88) 1.55
Panjari, M. (2009) 20.00 (14.97, 25.03) 3.11
Morales, A. (2009) 85.02 (40.09, 129.95) 1.28
Forsblad-d'Elia, H. (2009) 16.00 (11.22, 20.78) 3.12
Jankowski, C. M.(a) (2008) 31.70 (18.39, 45.01) 2.81
Jankowski, C. M.(b) (2008) -40.31 (-100.35, 19.73) 0.87
Igwebuike, A. (2008) -59.70 (-96.04, -23.36) 1.61
Gurnell, E. M.(a) (2008) 40.39 (-50.54, 131.32) 0.45
Gurnell, E. M.(b) (2008) 6.05 (3.39, 8.71) 3.15
Strous, R. D. (2007) -99.00 (-271.59, 73.59) 0.14
Poretsky, L. (2006) 0.00 (-126.82, 126.82) 0.25
Villareal, D. T.(a) (2006) 50.00 (-22.11, 122.11) 0.66
Villareal, D. T.(b) (2006) 100.00 (36.41, 163.59) 0.80
Martina, V. (2006) 182.11 (113.31, 250.91) 0.71
Schmidt, P. J.(a) (2005) -27.30 (-122.25, 67.65) 0.42
Schmidt, P. J.(b) (2005) 37.10 (29.66, 44.54) 3.05
Nordmark, G. (2005) 1.44 (-6.04, 8.92) 3.04
Williams, M. R. (2004) 54.75 (44.40, 65.10) 2.94
Dhatariya, K. (2005) 22.48 (19.16, 25.80) 3.14
Villareal, D. T.(a) (2004) 30.00 (-68.69, 128.69) 0.39
Villareal, D. T.(b) (2004) 100.00 (74.54, 125.46) 2.15
Acacio, B. D.(a) (2004) 88.00 (-10.26, 186.26) 0.39
Acacio, B. D.(b) (2004) -113.00 (-221.23, -4.77) 0.33
Kawano, H. (2003) 0.70 (-12.52, 13.92) 2.81
Kahn, A. J. (2002) -20.00 (-87.63, 47.63) 0.73
Jedrzejuk, D. (2003) 40.00 (-88.27, 168.27) 0.24
Assies, J. (2003) -11.00 (-282.70, 260.70) 0.06
Johannsson, G. (2002) -1.44 (-12.54, 9.66) 2.91
Carranza-Lira, S. (2002) -0.92 (-2.72, 0.88) 3.16
Lasco, A. (2001) -0.86 (-20.53, 18.81) 2.47
Barnhart, K. T. (1999) 225.00 (66.98, 383.02) 0.16
Morales, A. J.(a) (1998) -8.43 (-151.81, 134.95) 0.20
Morales, A. J.(b) (1998) 366.92 (205.05, 528.79) 0.16
Casson, P. R. (1995) 46.30 (42.07, 50.53) 3.13
Overall (I-squared = 97.9%, p = 0.000) 28.02 (21.44, 34.61) 100.00
NOTE: Weights are from random effects analysis
-529
0
529

Figure 2

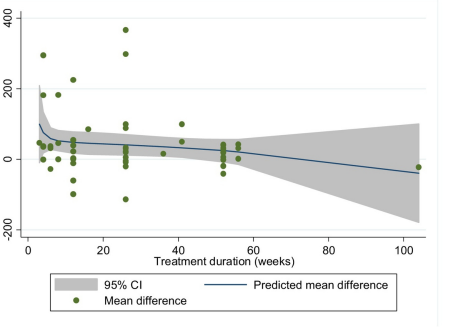
p= 0.034



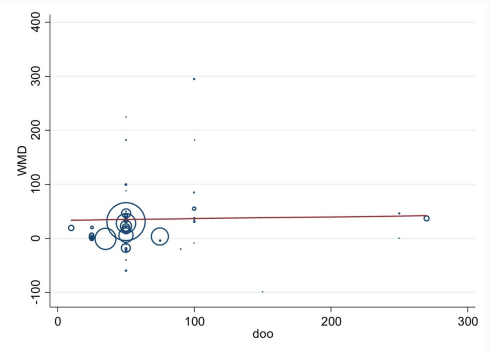
p= 0.773



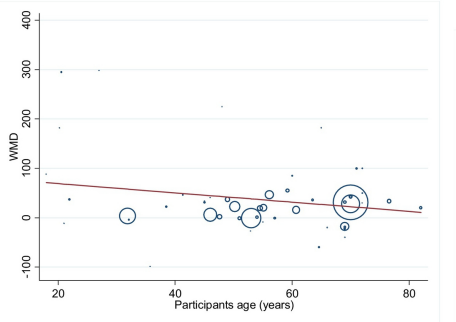
p= 0.293



p= 0.857



p= 0.151



p= 0.073

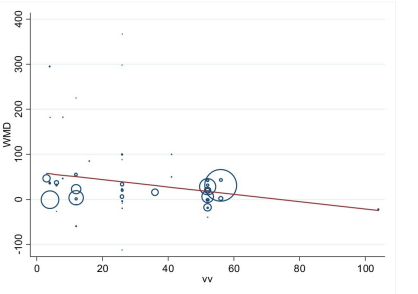


Figure 3

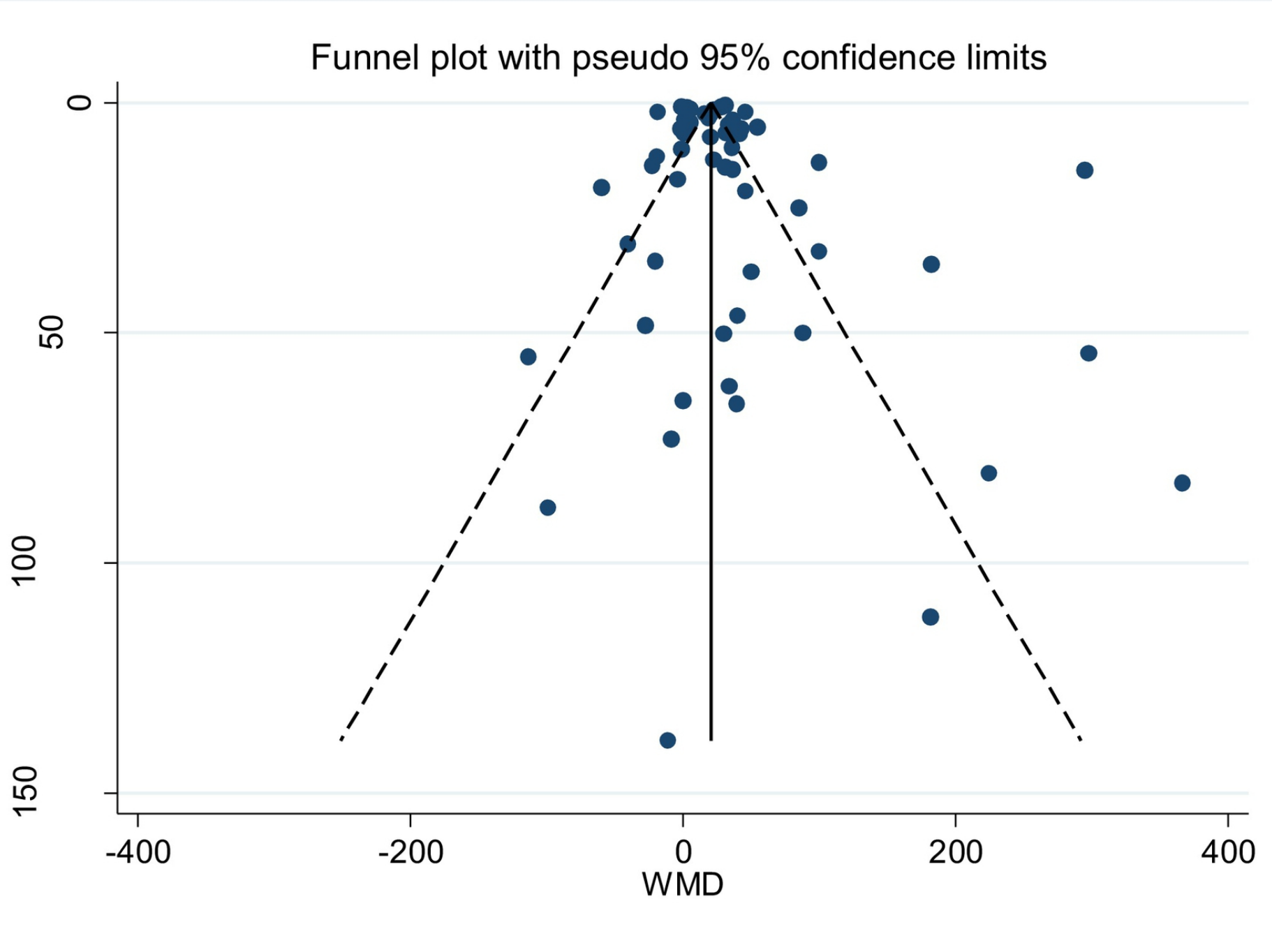

Funnel plot with pseudo 95% confidence limits
0
50
100
150
-400
-200
0
200
400
WMD

Figure 4