

Review

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Review

The Effect of Flaxseed Supplementation on Sex Hormone Profile in Adults: A Meta-Analysis

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Abstract: Flaxseed has been suggested as a viable solution to improve sex hormones. However, conflicting and uncertain evidence regarding its impact on sex hormone profiles exists. This meta-analysis assesses the effects of flaxseed on sex hormone profiles. PubMed, Scopus, Embase, and the Web of Science were searched for relevant articles in August 2021. The Cochrane Collaboration tool was used for the quality assessment, and the evidence's trustworthiness was assessed using the Grading of Assessment, Development, and Evaluation of Recommendations (GRADE). A total of ten articles revealed that flaxseed might not have a significant effect on follicle-stimulating hormone (FSH) ((WMD: 0.84; 95% CI: -5.53, 7.00, $p=0.791$; $I^2=88.6\%$, $p<0.001$, level of confidence: low), sex hormone-binding globulin (SHBG) ((WMD: 2.17; 95% CI: -1.19, 5.54, $p=0.206$; $I^2=66.3\%$, $p=0.011$, level of confidence: low), total testosterone (TT) (WMD: -0.00; 95% CI: -0.07, 0.07, $p=0.968$; $I^2=41.3\%$, $p=0.146$, level of confidence: low), free androgen index (FAI) (WMD: -0.13; 95% CI: -0.68, 0.42; $p=0.645$; $I^2=85.4\%$, $p<0.001$, level of confidence: low) and dehydroepiandrosterone sulfate (DHEAS) (WMD: 0.62; 95% CI: -3.35, 4.59, $p=0.761$; $I^2=63.6\%$, $p=0.064$, level of confidence: very low). It is demonstrated that flaxseed might not affect sex hormones in adults. Flaxseed supplementation had no significant effect on sex hormones in adults. Nevertheless, due to the limited included trials, this topic is still open and needs further studies in future RCTs.

Keywords: flaxseed; sex hormones; profile; meta-analysis

Introduction

Sex hormones, such as estrogens, androgens, and progestogens, are pivotal in regulating growth, metabolism, and reproduction [1]. Produced by the endocrine glands, these hormones are crucial for overall health [2]. Estrogen and progesterone are the primary female sex hormones, whose production and secretion are stimulated by pituitary hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In men, LH is the key hormone regulating testosterone. Beyond their roles in reproductive system regulation and maturation, these sex hormones significantly impact overall health. Estrogen, for instance, plays a protective role in maintaining bone density, supporting the immune system, and promoting cardiovascular health. Additionally, androgens contribute to muscle mass enhancement. However, imbalances can lead to various hormone-related diseases affecting both men and women, including polycystic ovary syndrome (PCOS), hypogonadism, and hormone-sensitive cancers like breast and prostate cancer [3,4]. These conditions often arise from either an excess or deficiency of specific hormones, significantly impacting quality of life [5]. For instance, reduced testosterone in men can lead to loss of muscle mass and strength, while estrogen imbalances in women can cause menstrual irregularities and increase cancer risk [6].

Diet can significantly impact circulating sex hormone levels, which is crucial for preventing hormone-related diseases [7]. Evidence suggests that flaxseed, rich in phytoestrogens like lignans,

may influence these hormone levels [8,9]. Lignans, a significant group of phytoestrogens, are known for their cancer-preventive properties [10]. Although they are present in low amounts across various plant foods, flaxseed stands out as the richest source, primarily containing secoisolariciresinol diglucoside (SDG) [11]. Upon ingestion, SDG is converted by intestinal bacteria into active mammalian lignans, enterodiols and enterolactone [12]. The levels of these enterolignans in the body are closely linked to dietary lignan intake [13]. Structurally similar to natural sex hormones, enterolignans exhibit mild hormonal effects and have been shown to inhibit cancer development in animal studies [14]. Lignans and flaxseed have been studied for their potential in preventing hormone-related cancers, especially breast cancer [15]. Epidemiologic research increasingly suggests that higher lignan intake is linked to a lower risk of breast cancer, particularly in postmenopausal women [16]. Because lignans have a structure similar to sex hormones, they can inhibit aromatase activity and increase the synthesis of sex hormone-binding globulin (SHBG) in adipose tissue and the liver [17]. Lignans can also bind to testosterone, promoting its excretion in bile [18]. Flaxseed consumption may alter estrogen metabolism in postmenopausal women, affecting serum levels of certain sex hormones and estrogen metabolites [19]. One study found that consuming five or 10 grams of ground flaxseed daily for seven weeks reduced estradiol levels [9]. Another clinical trial showed positive effects on sex hormones in overweight and obese women [20]. However, another study reported no significant changes in serum testosterone or SHBG levels with three grams of flaxseed daily for 12 weeks in patients with PCOS [21]. To provide an inclusive conclusion, the current study aimed to investigate whether flaxseed consumption can favorably alter sex hormones in adults.

Materials and Methods

"We followed the PRISMA guideline to conduct and report this review and meta-analysis [22]. "We registered our study protocol in PROSPERO, an international database of systematic reviews. (<http://www.crd.york.ac.uk/PROSPERO>, registration no: CRD42021331248).

Search Strategy

A systematic literature search conducted in online databases including PubMed, Scopus, Embase, and Web of science until August 2021 without language or any other limitations. The Medical Subject headings (MeSH) and non-MeSH keywords used to search the online databases briefly include 1) Sex hormone profile; 2) Flaxseed; 3) intervention, trial, randomized, randomized, random, randomly, placebo, assignment, clinical trial, RCT, clinical trials as Topic, cross-over, parallel. Two researchers independently screened the titles and abstracts to remove irrelevant studies, and any disagreements were resolved by other researchers. Additionally, any related studies published after the initial search were reviewed using alert services. Finally, potential related studies were checked using a search and by referencing the list of connected articles.

Eligibility Criteria

We included studies with these characteristics in our review and meta-analysis: a) RCT designs; b) participants must be adults over 18 years old; c) evaluated the effect of flaxseed supplementation; d) reported sex (hormones total testosterone, SHBG, FSH, free androgen index (FAI) and dehydroepiandrosterone Sulfate (DHEAS))) as primary or secondary outcomes. Moreover, studies excluded if: a) participants were in the age group of children and adolescents; b) did not have the interest outcomes of our study; c) they had no control group.

Data Extraction

Two investigators independently extracted data on the first author and the publication year, study location, number of subjects, study design, participant's baseline characteristics, study duration, type and dose of flaxseed supplement in the intervention and control groups, as well as the mean and standard deviation (SD) of outcome data. We consulted other authors to resolve any disagreements between reviewers.

Risk of Bias Assessment and Meta-Evidence

We evaluated the quality of eligible trials based on the Cochrane Collaboration's tool for systematic reviews of interventions, which contains the following domains: randomization process, deviations from the intended interventions, deviations from the planned interventions, missing outcome data, measurement of the outcome, and selection of the reported result [23]. We employed the GRADE approach to evaluate the included RCTs' credibility rigorously. As a result, the evidence is systematically classified into four distinct categories: high, moderate, low, or very low [24].

Statistical Analysis

We used the weighted mean difference (WMD) and 95% confidence intervals to measure the effect size statistic of sex hormones for meta-analysis. The random effect model was used to conduct all meta-analyses. The heterogeneity between studies was examined by the Cochrane Q test and I^2 statistic [25]. In addition, we conducted subgroup analysis based on mean age, duration, dosage of flaxseed and quality of studies to investigate possible sources of heterogeneity. Sensitivity analyses were carried out to explore the robustness of meta-analysis and comparison the overall effect [26]. No small-study effect analysis was conducted for any of the outcomes since none of them included at least 10 studies [27]. All statistical analyses were performed using STATA version 11.2 (Stata Corp, College Station, TX) and P-values less than 0.05 were considered as statistically significant.

Results

Literature Search and Study Characteristics

We found a total of 1215 records from databases and hand searches during our search for relevant clinical trials. After removing duplicates and non-article documents, we were left with 824 studies to screen the titles and abstracts. Out of these, 810 studies were found to be irrelevant and were excluded. Subsequently, we reviewed 14 full texts of articles for further assessment (**Figure 1**). Finally, we included 10 randomized controlled trials (RCTs) in our systematic review and meta-analysis [19,21,28–35]. All the RCTs included in the analysis were conducted from 1998 [28] to 2020 [21]. Five of the ten included studies were carried out in the USA [28–31,33], two in Iran [21,35], two in Brazil [32,34], and one in Canada [19]. The duration in the trials varied from 5 to 24 weeks. The average age of the participants was 50 years, and the sample sizes for both the patient and control groups ranged from 34 to 81.

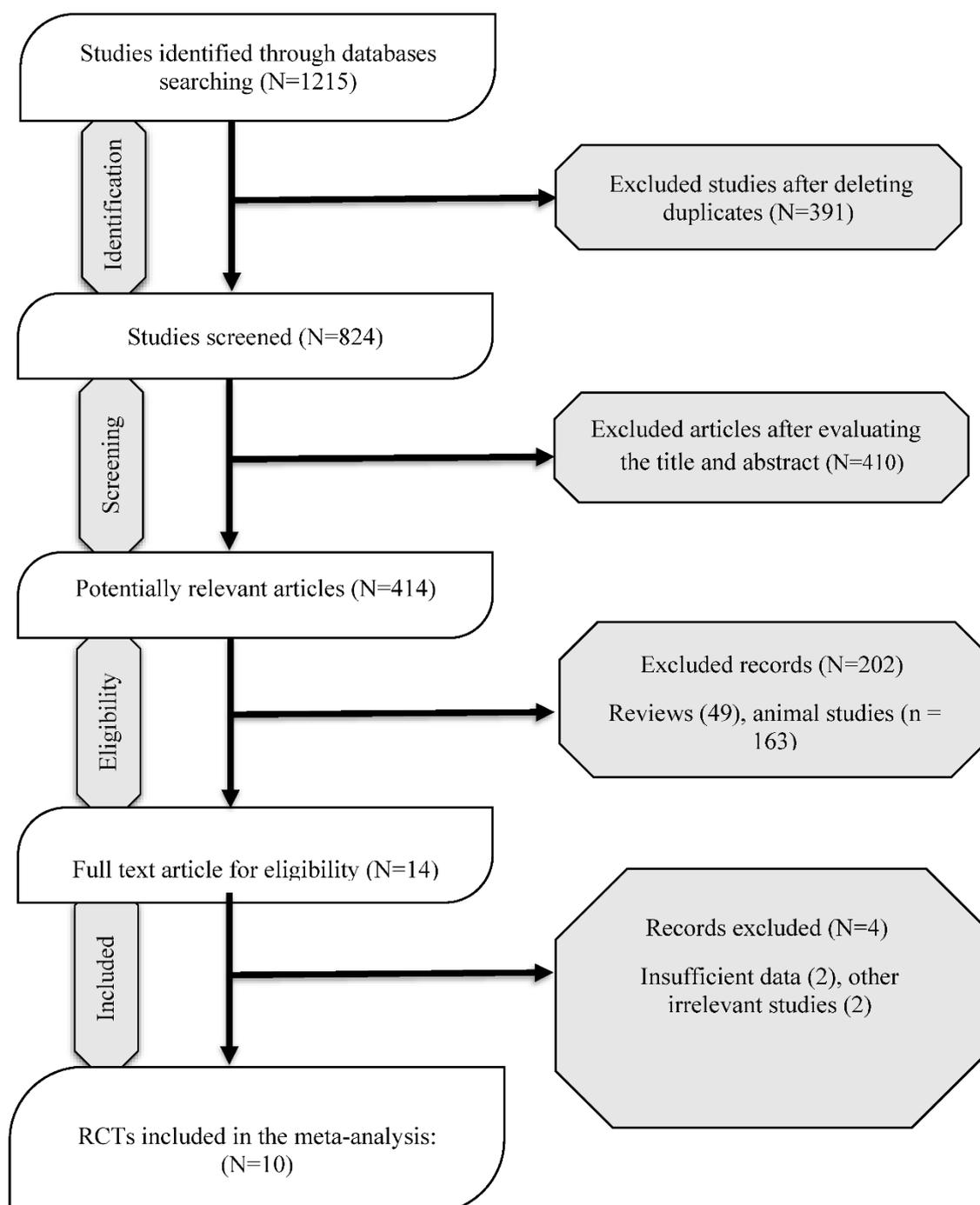


Figure 1. Flow diagram of study selection.

Quality Assessment and Grade Approach

The quality of included studies is presented in **Table 2**. Only six of the ten included studies showed a low risk of bias [19,21,28,32,33,35]. The overall quality assessment for five studies was high risk, mainly since outcome assessors were not blinded [19,21,31,32,34]. Most studies had some concern risk of bias based on other sources of bias about their method [19,21,30,31,33,34]. All outcomes have low-quality evidence according to the GRADE approach.

Included study	Arjmandi, 1998.	Lucas, , 2002	Demark-Wahnefried, USA, 2008	Patade, USA, 2008	Simbalista, Brazil, 2009	Vargas, USA, 2011	Colli, Brazil, 2012	Mirmasoum i, Iran, 2017	Chang, Canada, 2018	Haidari, Iran, 2020
Year	2020	2020	2013	2008	2019	2021	2021	2017	2019	2018
Location**	USA	USA	USA	USA	Brazil	USA	Brazil	Iran	Canada	Iran
Duration (week)	6	12	5	12	12	6	24	12	7	12
Mean dosage of flaxseed /Intervention	38g/day Whole Flaxseed	40 g/day Ground Whole Flaxseed	30 g/day Flaxseed-Supplemente d Die	30 g/day Flaxseed	25 g/day Ground Flaxseed	3.5 g/day Flaxsee d Oil	1g/d Flaxseed Extract	1 g/day Flaxseed Oil	15 g/day Ground Flaxseed	30 g/day Brown Milled Flaxseed Powder + Lifestyle Modificatio n
Target population	Postmenopaus al Women	Postmenopaus al Women	Prostate Cancer	Postmenopaus al Women	Postmenopaus al Women	PCOS	Menopaus al	PCOS	Postmenopausa l Women	PCOS
Participants' age (year)	56	54	60	47-63	52	29	54	28	60	27
Participants' sex	Women	Women	Men	Women	Women	Women	Women	Women	Women	Women
Control group	Sunflower Seed	Wheat	Usual Diet	Control	Wheat Bran	Soybea n Oil	Collagen	Liquid Paraffin	Usual Diet	Lifestyle Modificatio n

Table 2. Results of risk of bias assessment.

Study	Random Sequence Generation	Allocation concealment	Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias
Arjmandi, US, 1998	L	U	L	L	L	L	H
Lucas, USA, 2002	L	U	L	H	L	L	L
Wahnefried, USA, 2008	L	U	L	H	L	H	L
Patade, USA, 2008	L	U	L	H	L	H	L
Simbalista, Brazil, 2009	L	L	L	H	L	L	L
Vargas, USA, 2011	L	L	L	H	L	L	L
Colli, Brazil, 2012	L	U	H	H	U	U	L
Mirmasoumi, Iran, 2017	L	L	L	L	L	L	L
Chang, Canada, 2018	L	L	L	L	L	H	L
Haidari, Iran, 2020	L	L	L	L	U	U	L

Meta-Analysis Results

Flaxseed on Sex Hormones Profile

Regarding the effects of flaxseed on sex hormone-related indicators in adults, we found no significant change in DHEA (WMD: 0.62; 95% CI: -3.35, 4.59, $p=0.761$; $I^2=63.6%$, $p=0.064$) (**Figure 2**), FSH (WMD: 0.84; 95% CI: -5.53, 7.00, $p=0.791$; $I^2=88.6%$, $p<0.001$) (**Figure 3**), SHBG (WMD: 2.17; 95% CI: -1.19, 5.54, $p=0.206$; $I^2=66.3%$, $p=0.011$) (**Figure 4**), TT (WMD: -0.00; 95% CI: -0.07, 0.07, $p=0.968$; $I^2=41.3%$, $p=0.146$) (**Figure 5**), and FAI (WMD: -0.13; 95% CI: -0.68, 0.42; $p=0.645$; $I^2=85.4%$, $p<0.001$) (**Figure 6**). Flaxseed supplementation improved FSH, and SHBG, in in high-quality studies, and long intervention durations (≥ 8 weeks), respectively (**Table 3**). Sensitivity analyses showed that removing any specific trial related to outcomes did not influence the results.

Table 3. Subgroup analyses for the effects of Flaxseed supplementation on sexual hormone.

	Number	WMD (95% CI)	P-within	I ² (%)	P-heterogeneity
FSH					
Overall	5	0.84 (-5.53, 7.00)	0.791	88.6	<0.001
Age(year)					
≤50	3	1.39 (-7.70, 10.48)	0.764	93.3	<0.001
>50	2	-0.01 (-9.54, 9.51)	0.998	80.0	<0.001
Dose (g/day)					
<30	2	-0.96 (-12.93, 11.02)	0.876	95.0	<0.001
≥30	3	2.19 (-4.77, 9.16)	0.537	77.0	0.013
Quality					
Low	2	-6.48 (-9.34, -3.63)	<0.001	0.0	0.513
High	3	5.48 (2.68, 8.27)	<0.001	0.0	0.920
Duration (week)					
<8	1	4.92 (-1.32, 11.16)	0.123	-	-
≥8	4	-0.09 (-7.26, 7.07)	0.981	90.6	<0.001
SHBG					
Overall	6	2.17 (-1.19, 5.54)	0.206	66.3	0.011
Age(year)					
≤50	4	4.94 (-0.10, 9.99)	0.055	68.9	0.022
>50	2	-1.76 (-5.57, 2.04)	0.634	29.8	0.233
Dose (g/day)					
<30	3	0.43 (-4.96, 5.81)	0.887	66.4	0.051
≥30	3	4.36 (-1.59, 10.31)	0.114	73.5	0.023
Quality					
Low	2	0.79 (-3.06, 4.64)	0.687	0.0	0.361
High	4	2.73 (-2.23, 7.69)	0.280	78.5	0.003

Duration (week)						
<8	3	-0.31 (-2.76, 2.14)	0.806	38.1	0.199	
≥8	3	7.78 (3.60, 11.95)	<0.001	0.0	0.763	
<hr/>						
Total testosterone						
Overall	5	-0.00 (-0.07, 0.07)	0.968	41.3	0.146	
Age(year)						
≤50	3	0.00 (-0.03, 0.03)	0.994	0.0	0.980	
>50	2	13.84 (-18.31, 45.98)	0.399	84.5	0.012	
Dose (g/day)						
<30	2	-0.00 (-0.07, 0.07)	0.949	0.0	0.554	
≥30	3	0.10 (-0.95, 1.15)	0.851	69.0	0.040	
Quality						
Low	2	13.90 (-17.91, 45.72)	0.957	84.4	0.011	
High	3	-0.00 (-0.07, 0.07)	0.999	0.0	0.845	
Duration (week)						
<8	3	0.04 (-1.31, 1.38)	0.392	70.2	0.035	
≥8	2	0.00 (-0.03, 0.03)	0.963	0.0	0.999	
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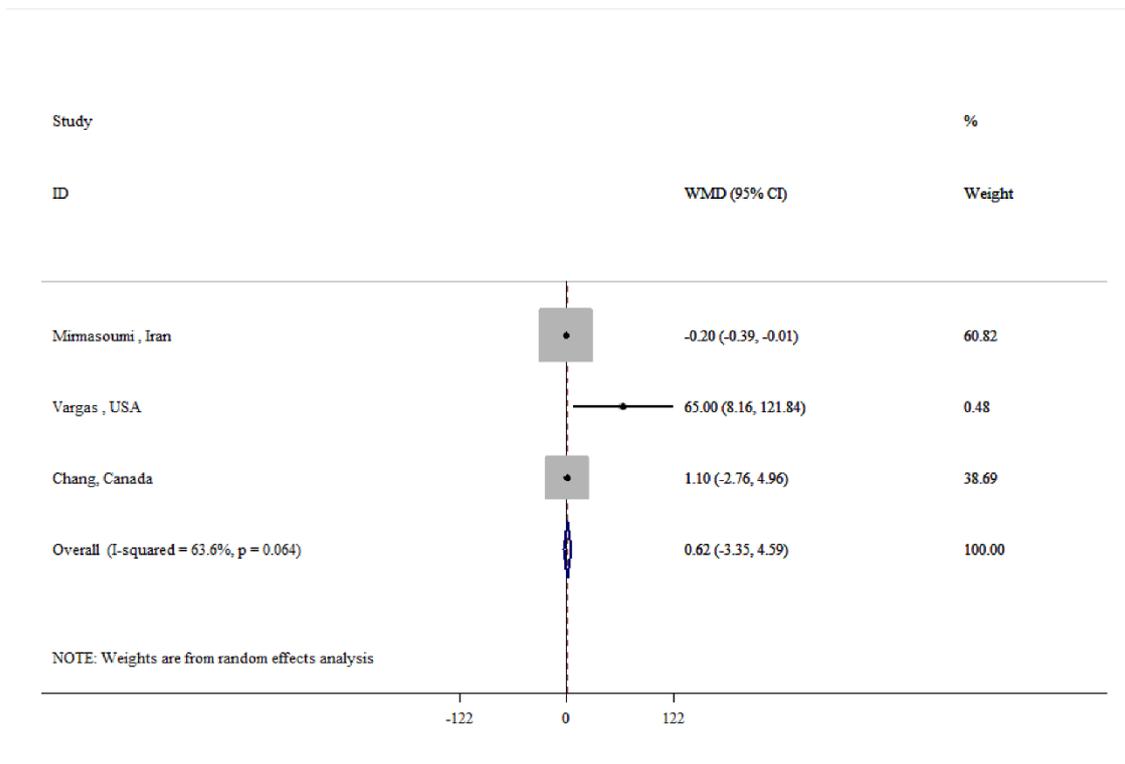


Figure 2. Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on DHEAS.

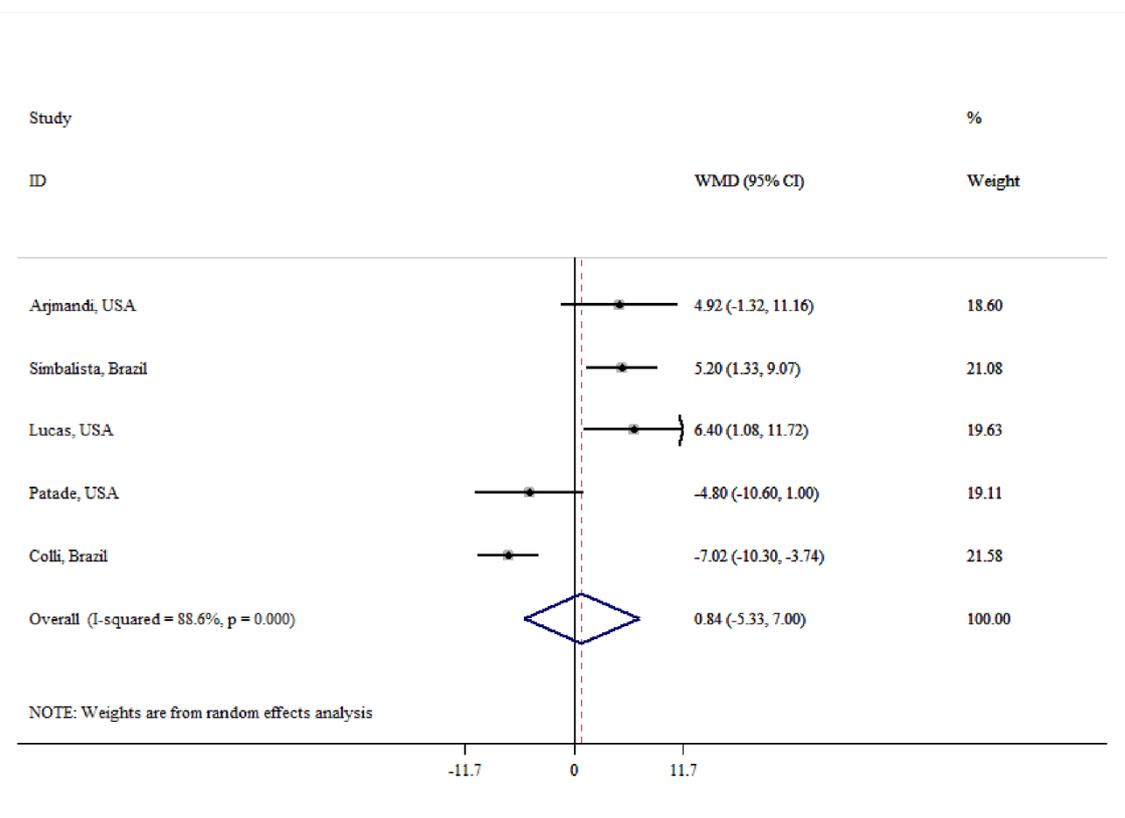


Figure 3. Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on FSH.

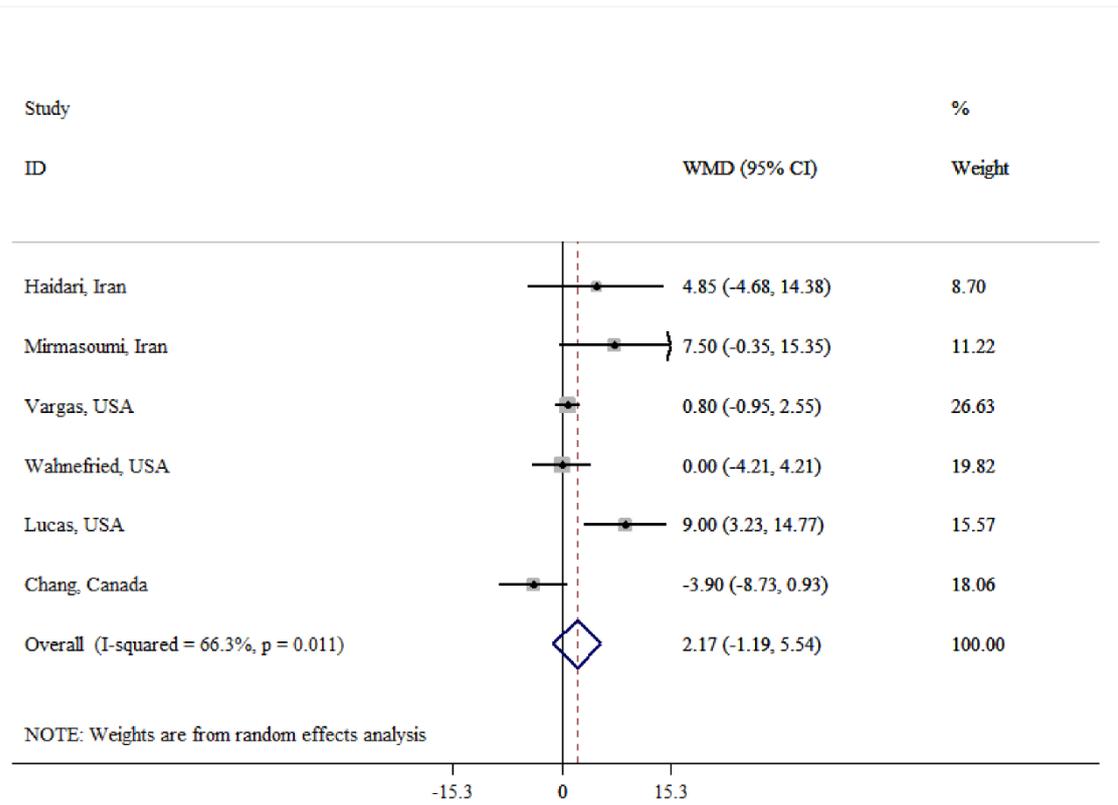


Figure 4. Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on SHBG.

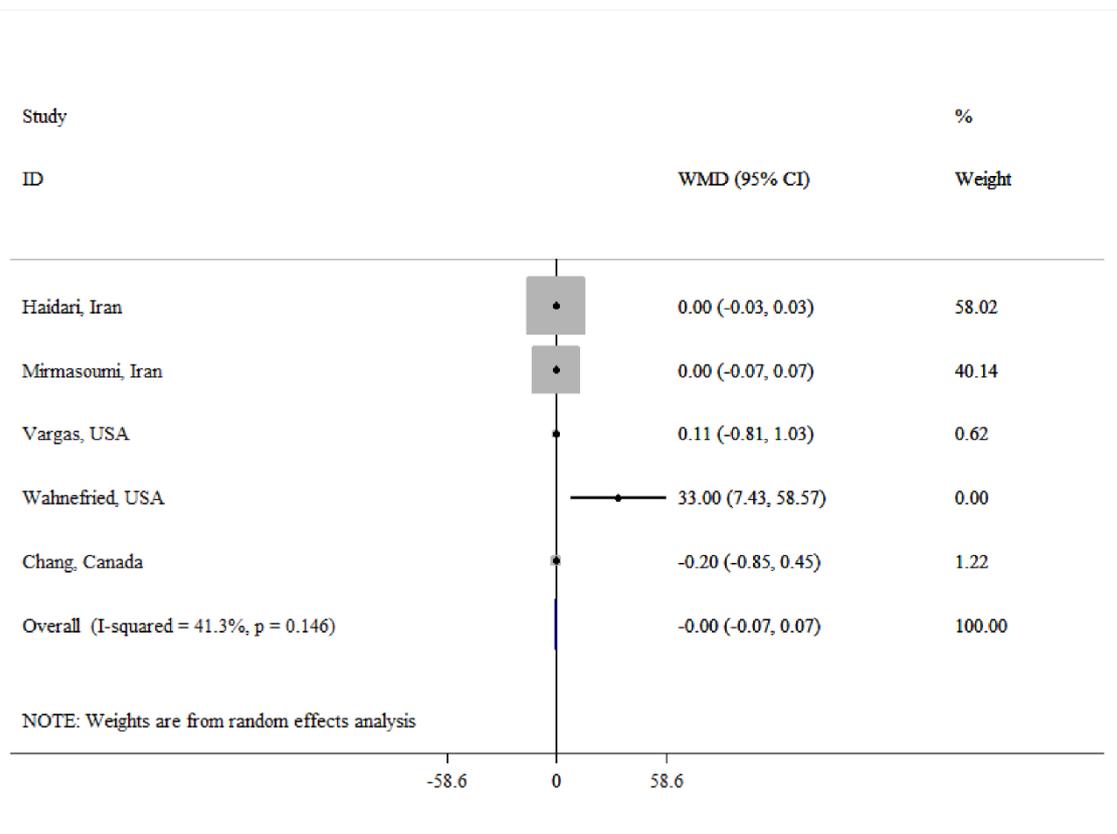


Figure 5. Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on TT.

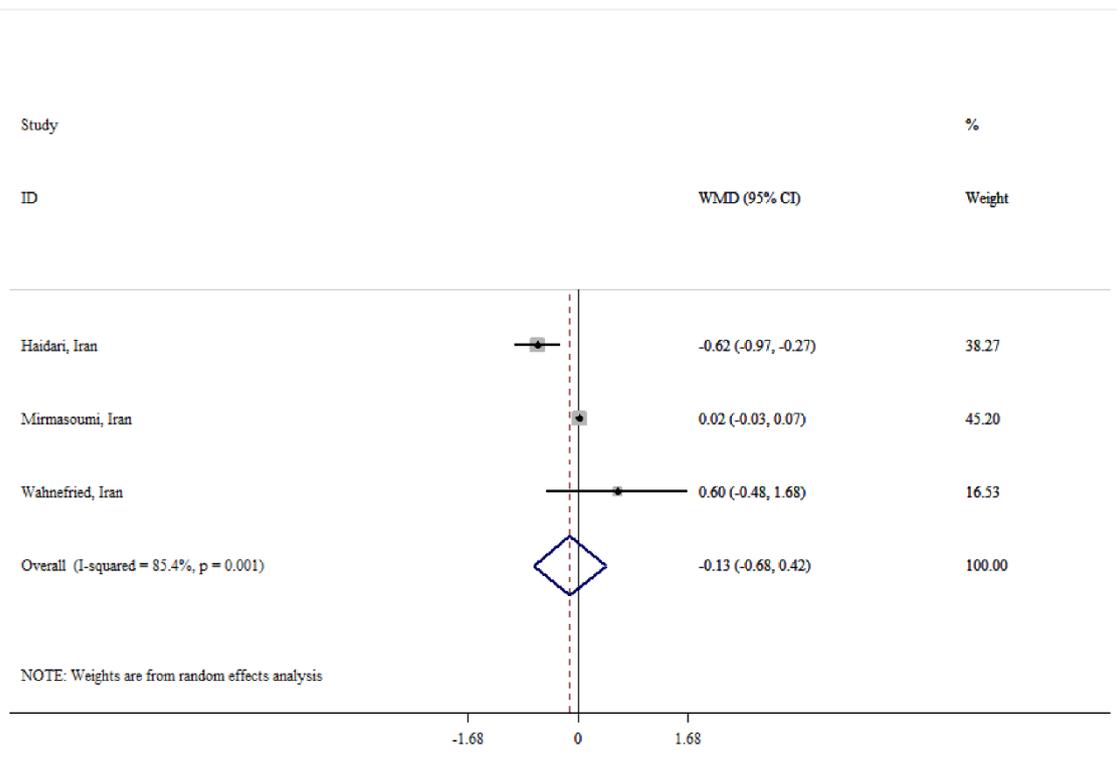


Figure 6. Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on FAI.

Discussion

This is the first meta-analysis of the effect of flaxseed supplementation on sex hormones status in adults. We found no significant alterations in FSH, FAI, DHEAS, TT, and SHBG. In addition, subgroup analyses revealed that flaxseed supplementation significantly increased SHBG in individuals aged 50 or younger, those with PCOS, and those who underwent the intervention for at least 12 weeks. Additionally, an increase in TT was observed in men and individuals with prostate cancer following flaxseed supplementation.

Dietary components can significantly impact circulating sex hormone levels, which is crucial for preventing hormone-related issues. The endocrine system, a complex network of hormones and glands, declines with age, leading to a yearly reduction in testosterone levels by 0.5–1% in men and a decrease in estrogen levels in women starting around age 30. In men, this TT decline is associated with loss of muscle mass and strength, and supplementation with testosterone or dihydrotestosterone can enhance muscle strength. Flaxseed, rich in biologically active compounds like secoisolariciresinol diglucoside, is metabolized by intestinal bacteria into mammalian lignans, enterolactone, and enterodiols. These compounds are structurally similar to natural sex hormones and have demonstrated weak hormonal effects and cancer-preventive properties in animal studies. For over two decades, flaxseed and lignans have been studied for their potential to prevent hormone-related cancers, including breast cancer. Additionally, lignans have been shown to reduce testosterone levels by binding to enterohepatic circulation and inhibiting 5 α -reductase, the enzyme that converts testosterone to dihydrotestosterone.

Research indicates that diets high in lignans may help protect against prostate cancer, which is linked to high androgen levels. Lignans have also been shown to stimulate SHBG synthesis in the liver and interact with SHBG, altering the biological activity of circulating androgens and estrogens. However, our study did not find significant effects of flaxseed consumption on FSH, FAI, and DHEAS levels in adults. This could be due to inconsistencies in the trials, such as varying durations, forms, and doses of flaxseed supplements. The heterogeneity in these trials, particularly regarding intervention duration, might mean that shorter periods are insufficient to produce significant changes in sex hormone levels. Additionally, the small sample sizes in the included trials may have resulted in low statistical power, making it difficult to detect significant effects. This highlights the need for further research with larger sample sizes and consistent methodologies. In line with two other studies on postmenopausal women, our research found that flaxseed intake did not affect serum levels of TT, androstenedione, or DHEAS [9,36]. Cross-sectional studies have shown mixed results, with some reporting positive, negative, or no correlation between enterolignans and androgens [37]–[40]. Lignans might influence androgen metabolism by inhibiting 5 α -reductase, which converts testosterone to the more potent dihydrotestosterone, and by inhibiting aromatase, which converts androgens to estrogens [41]. Additionally, lignans can stimulate SHBG synthesis in the liver and interact with SHBG to modify the biological activity and availability of circulating estrogens and androgens [42,43]. Observational studies have found positive correlations between lignans and SHBG [17], but our findings, like other intervention studies, do not support flaxseed's role in altering SHBG levels [9,29,36]. Regarding the estrogenic effects of flaxseed, our study found no changes in FSH or FAI levels, which contradicts earlier findings suggesting that flaxseed has estrogenic properties. It's important to note that only a few RCTs have investigated the impact of flaxseed supplementation on sex hormones. Therefore, more RCTs are needed to draw definitive conclusions about the effects of flaxseed on sex hormones across various durations and doses. Haggans et al. [44] observed that consuming 10 g of flaxseed daily for 7 weeks significantly raised the urinary levels of 2-hydroxyestrone and the 2:16 α -hydroxyestrone ratio. Similarly, McCann et al.'s [45] pre-post study found significant increases in these urinary markers in women who took 10 g of flaxseed daily for 7 days. In a randomized controlled trial by Brooks et al. [46], daily intake of a flaxseed muffin (containing 25 g of flaxseed) for 16 weeks also significantly boosted the urinary 2-hydroxyestrone

and 2:16 α -hydroxyestrone ratio. While the exact mechanisms remain unclear, it is suggested that flaxseed and lignans might influence estrogen metabolite profiles by altering the expression or activity of cytochrome P450 enzymes, which are responsible for estrogen hydroxylation [45,47]. For instance, flaxseed supplementation in hens increased CYP1A1 expression, leading to higher production of 2-hydroxyestrone and lower production of 16 α -hydroxyestrone. Although the 2:16 α -hydroxyestrone ratio has been inversely linked to breast cancer risk and proposed as a dietary intervention target [47], recent studies suggest that the overall and relative levels of metabolites from the 2-, 4-, and 16-hydroxylation pathways might be more relevant for breast cancer risk and prevention [48,49]. In our study, flaxseed intake did not significantly affect the levels of FSH, FAI, DHEAS, TT, and SHBG in the bloodstream. This aligns with other studies on serum, plasma, or urinary estrogen levels in postmenopausal women [29,36,46], except for one crossover trial that found significant reductions in serum estradiol and estrone sulfate with 10 g of flaxseed per day for seven weeks [32]. Since estradiol and estrone are linked to higher postmenopausal breast cancer risk, reducing their levels could be protective. *In vitro* studies suggest that lignans might lower estrogen synthesis by inhibiting the aromatase enzyme, which converts testosterone and androstenedione into estradiol and estrone [50,51].

Limitations

The current meta-analysis has some limitations. Firstly, the number of RCTs evaluating the effect of flaxseed consumption on sex hormones status in adults is limited at present. This may limit the power of our analyses and therefore, the results should be interpreted in the context of constraints in available data. Secondly, high heterogeneity among studies could not be fairly expounded after performing the subgroup analysis. Therefore, the reliability of the results may be adversely influenced.

Conclusions

Our findings indicate that flaxseed does not significantly impact sex hormones in adults. However, given the limitations of the trials reviewed, further research through future RCTs is necessary to explore this topic more thoroughly.

Author Contributions: Conceptualization and Methodology: A.A, A.K., M.H.H., Data curation, Formal analysis, Software: A.K., N.D., S.S., Writing – original draft: A.K., M.H.H., S.S., All authors have read and approved the manuscript.

Data Availability: Data described in the manuscript are available from the Corresponding author, upon reasonable request.

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Conflicts of Interest: The authors declare no competing interests.

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