

INVITED REVIEW

The effect of vitamin D supplementation on the androgenic profile in men: A systematic review and meta-analysis of clinical trials

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Abstract

The aim of this systematic review and meta-analysis was to evaluate the effect of vitamin D supplementation on total testosterone (TT) and sex hormone-binding globulin (SHBG) in men. We searched PubMed, Scopus and Web of Science for randomized, controlled trials of vitamin D supplementation in men ≥ 18 years old up to September 2018, without language restrictions. Meta-analysis was based on a random effects model. The systematic review was registered as CRD42018094498. We identified 3,402 articles, of which eight studies with 10 effect sizes met the inclusion criteria. Vitamin D daily dose equivalents ranged from 600 to 4,000 per day to 60,000 IU per week; duration was 6 weeks to 36 months. In general, vitamin D supplementation had no significant effect on TT (MD = 0.20, 95% CI: -0.20, 0.60, $p = 0.336$) and SHBG (MD = 1.56, 95% CI: -0.85, 3.97, $p = 0.204$). Subgroup analysis conducted with duration of prescription, type (daily or weekly), dosing frequency and baseline vitamin D and TT concentration showed that vitamin D did not significantly affect TT. The present study did not find any evidence to support beneficial effect of vitamin D supplementation on TT and SHBG in men. Thus, further large-scale randomised controlled trials are required to evaluate the effects of vitamin D supplementation on androgen in men.

KEYWORDS

men, sex hormone-binding globulin, total testosterone, vitamin D

1 | INTRODUCTION

Vitamin D deficiency is a common health concern. More than 1 billion people in all over the world suffer from vitamin D deficiency, according to global estimation (Holick & Chen, 2008). Over the past two decades, the prevalence of vitamin D deficiency has increased in countries with tropical climate in Asia, at around 30%–93% (Heshmat et al., 2008). According to another study, about 40%–100% of the American and European elderly people who are not in health centres suffer from vitamin D deficiency (Holick et al., 2005).

Numerous studies have emphasised that vitamin D plays significant roles in preventing several disorders such as hypertension, cardiovascular diseases, stroke, diabetes, cancers, autoimmune diseases and infertility (Chowdhury et al., 2014; Hagenau et al., 2009; Pilz et al., 2008; Pludowski et al., 2013; Wehr et al., 2009). Vitamin D generally is known for its regulatory functions in calcium homeostasis and bone health; however, vitamin D activities are beyond those previously mentioned (Fleet, 2008).

Previous studies have shown that vitamin D, apart from its beneficial effects on musculoskeletal health, is involved in the regulation

of reproductive function (Karras, Anagnostis, Kotsa, & Goulis, 2016). The expression of vitamin D metabolising enzymes and vitamin D receptor in several parts of the male reproductive system suggested the effect of vitamin D on the male reproductive system (Jensen, 2012). This concept was supported by an experimental study which indicated vitamin D improved the number of functional spermatozoa, histological abnormalities and hypogonadism in mice (Kinuta et al., 2000).

Furthermore, vitamin D may have beneficial effects on hormonal production in the male reproductive system. To achieve this, testosterone, an anabolic hormone that is produced by Leydig cells after LH (luteinising hormone) secretion has a great impact on the reproductive system, sexual function, bone health, fat metabolism and muscle mass (Hagenau et al., 2009; Pludowski et al., 2013). Testosterone that decreases with age is associated with musculoskeletal system diseases, including sarcopenia and osteopenia (Marcell, 2003) and also causes higher rates of mortality (Khaw et al., 2007; Lerchbaum et al., 2012). Therefore, it may be worth mentioning that vitamin D and testosterone deficiency have similar complications as above. In addition to these statements, the fact that vitamin D is strongly associated with androgen levels in men has been supported in previous studies (Chen et al., 2008; Wehr et al., 2010; Wu et al., 2008).

Therefore, under the potential positive effect of vitamin D on androgens, we aimed to do a systematic review and meta-analysis of controlled clinical trials to provide the evidence for the effect of vitamin D on testosterone.

2 | METHODS

2.1 | Bibliography search strategy

Our meta-analysis review was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Liberati et al., 2009). The systematic review was registered as CRD42018094498 in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>).

PubMed, Scopus and Web of Science were searched up to September 2018 with no limitation of language and time of publication using the following Mesh and non-Mesh keywords: (vitamin D OR 25-hydroxy vitamin D OR 25(OH)D OR 1,25(OH)D OR vitaminD3 OR 1,25(OH)2D3 OR ergocalciferol OR cholecalciferol OR calcitriol OR calcifediol) AND (testosterone OR anabolic steroids OR male sex hormone OR total testosterone) AND (sex hormone-binding globulin (SHBG) OR sex hormone-binding globulin).

Two researchers (EHM and MM) reviewed the papers independently and discussed any discrepancies in the included studies. Furthermore, we searched the references of all eligible original articles, reviews and other relevant articles manually.

2.2 | Eligibility criteria

Papers were included if they (a) were original articles, (b) were RCTs, (c) were conducted on men ≥ 18 years old, (d) were supplementation

with vitamin D or analogs, (e) consisted of vitamin D with other supplements such as calcium in both the intervention and placebo group, although, we were able to extract the pure effect of vitamin D and (f) assessed serum total testosterone (TT) or SHBG as compared with placebo.

Exclusion criteria were as follows: (a) they were animal studies, nonrandomised or noncontrolled trials, observational studies, cases, letters, editorials or systemic reviews, (b) they were performed on men <18 years old and women and (c) they evaluated the acute effect of vitamin D supplementation on TT.

2.3 | Data extraction

The researchers (EHM and MM) screened literature and extracted information from eligible studies. The extracted data were as follows: first author, year of publication, design of trials, location, age and health status of participants, sample size, dosage, type and prescription method of vitamin D, duration of intervention, baseline 25(OH) D concentration, baseline 25(OH) D concentration and related data of outcome variables.

2.4 | Assessment of quality

Two researchers (EHM and AG) independently used the Cochrane Handbook for Systematic Reviews of Interventions to Qualify Trials (Higgins et al., 2011). Criteria for evaluation studies were as follows: randomisation methods; allocation concealment; blinding methods, integrity of data, and selective reporting bias and other sources of bias. Any disagreement was resolved with consensus or consultant with the second author (MM). Each item was classified as low, high and unclear (if there was unclear information). The overall quality of studies was graded as "good" if there were low risk of bias for more than two items, "fair" if there were low risk of bias for two items and "poor" if there were low risk of bias for less than two items.

2.5 | Statistical analysis

Data were provided in a summary table with narrative information about each study. For estimating the pooled effect, mean change (MDs) with their standard deviations (SDs) for TT and SHBG of each study were obtained to calculate the mean difference and its SE (standard error) between vitamin D supplemented and control groups. The effect of vitamin D on TT and SHBG was estimated by the weighted mean difference (WMD) with corresponding 95% confidence intervals for continuous outcomes (TT and SHBG). Meta-analysis was performed using a random effects model. A difference of characteristics in study populations, dosage of supplement, intervention duration and baseline serum 25(OH) vitamin D levels confirmed the heterogeneity and assumption of the random effects model. Heterogeneity in the study results was assayed with the Cochran's Q test and quantified with the I² statistic (Higgins & Green, 2011). A subgroup analysis was also performed based on study duration (<16 or ≥ 16 weeks), type of vitamin D prescription (daily or weekly),

vitamin D supplementation dose $<3,000$ mg/day or $\geq 3,000$ mg/day and baseline serum 25(OH)D and TT levels. Sensitivity analysis was carried out to explore the effect of one study on the overall estimate. Publication bias was assessed by using asymmetry tests (Egger's test; Egger, Smith, Schneider, & Minder, 1997). All statistical analyses were performed using STATA version 11.2 (Stata Corp). p -Value <0.05 was considered statistically significant.

2.5.1 | NutriGrade

To judge the overall quality of meta-analysis for the effect of vitamin D supplementation on TT and SHBG, the NutriGrade scoring system was used (Schwingshackl et al., 2016) (scored 0 up to 10). Meta-analysis of the randomised controlled trial of this tool was followed with these criteria: (a) risk of bias, (b) precision, (c) heterogeneity, (d) directness, (e) publication bias, (f) funding bias and study design. Four category was suggested to evaluate the credibility of evidence based on this scoring tool: (a) high (≥ 8 points), (b) moderate (6–7.99 points), (c) low (4–5.99) and (d) very low if (0.3–99 points).

3 | RESULTS

3.1 | Study characteristics

The flow chart of the literature search is shown in Figure 1. A total of 3,402 articles were retrieved from the first databases search along with two studies added by hand search, of which one included three effect sizes (Heijboer et al., 2015). After removing duplicates, 2,875

records remained to be screened by title and abstract and 2,862 were excluded. Of the 13 articles reminded for more screening, five studies were excluded, which were explained by reason as shown in Figure 1. Thus, eight studies with 10 effect sizes met our eligibility criteria for quantitative synthesis.

Table 1 shows the descriptive data for the included studies. All the eight studies conducted for meta-analysis were published in English and were double-blind RCTs. However, two of the double-blind studies were factorial design (Saha & Goswami, 2018; Scholten et al., 2015). All the trials were published from 2008 to 2018. The included studies comprised 1,061 participants who were male. Most of the studies were conducted in European countries (Lerchbaum et al., 2017; Heijboer et al., 2015; Jorde et al., 2013; Lerchbaum et al., 2018; Pilz et al., 2011; Zittermann et al., 2018). Five studies included healthy participants living independently, except for three studies involving patients with heart disease (Schroten et al., 2013; Zittermann et al., 2018) and included subjects living in nursing homes (Chel, Wijnhoven, Smit, Ooms, & Lips, 2008).

Oral supplementation with cholecalciferol was used in all the studies with different doses ranging from 600 to 4,000 per day to 60,000 IU per week. The intervention period varied from 6 to 144 weeks. In one study, oral cholecalciferol and calcium were co-supplemented (Jorde, Sneve, Torjesen, & Figenschau, 2010).

3.2 | Assessment of the risk of bias

Risk of bias assessment was performed with Cochran collaboration tools as displayed in Table 2. All the studies explicitly

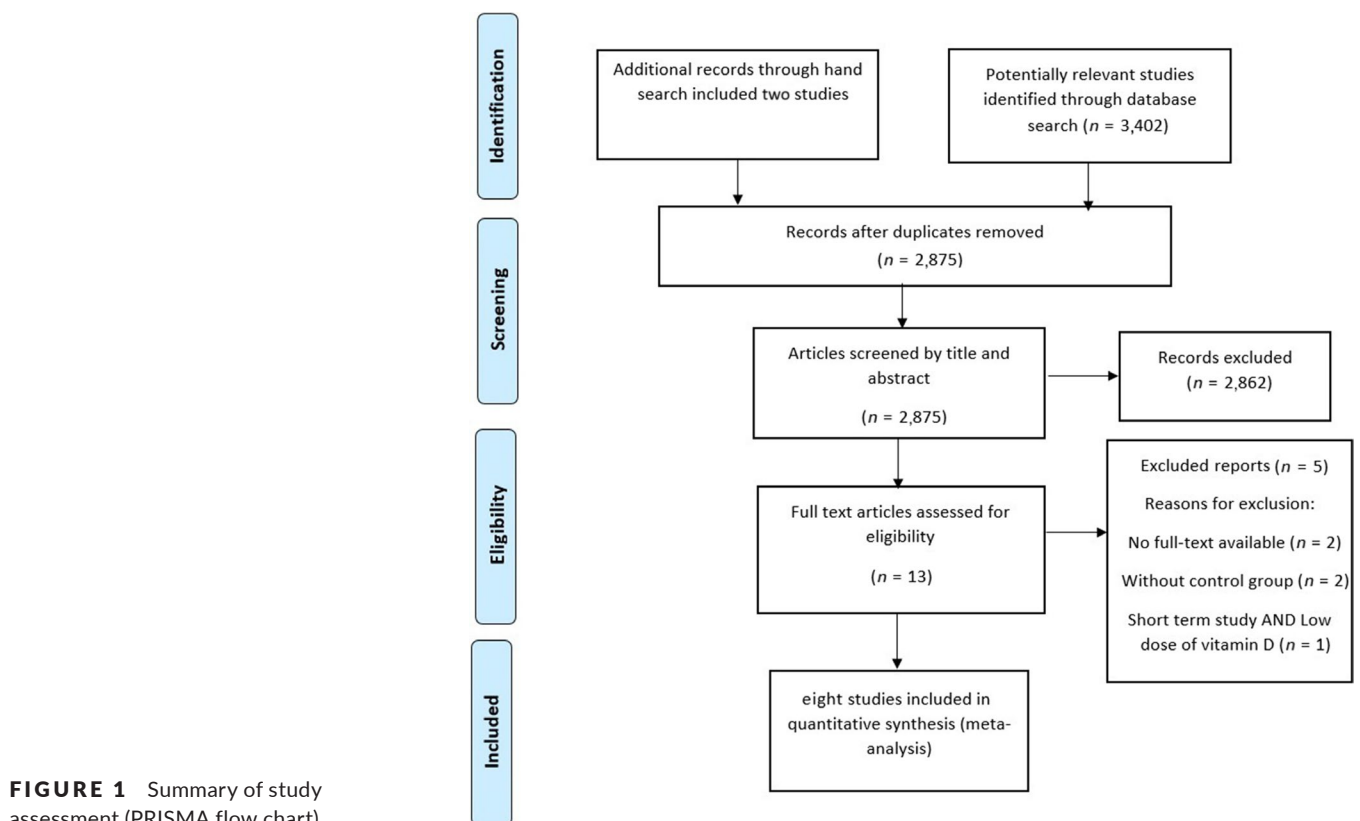
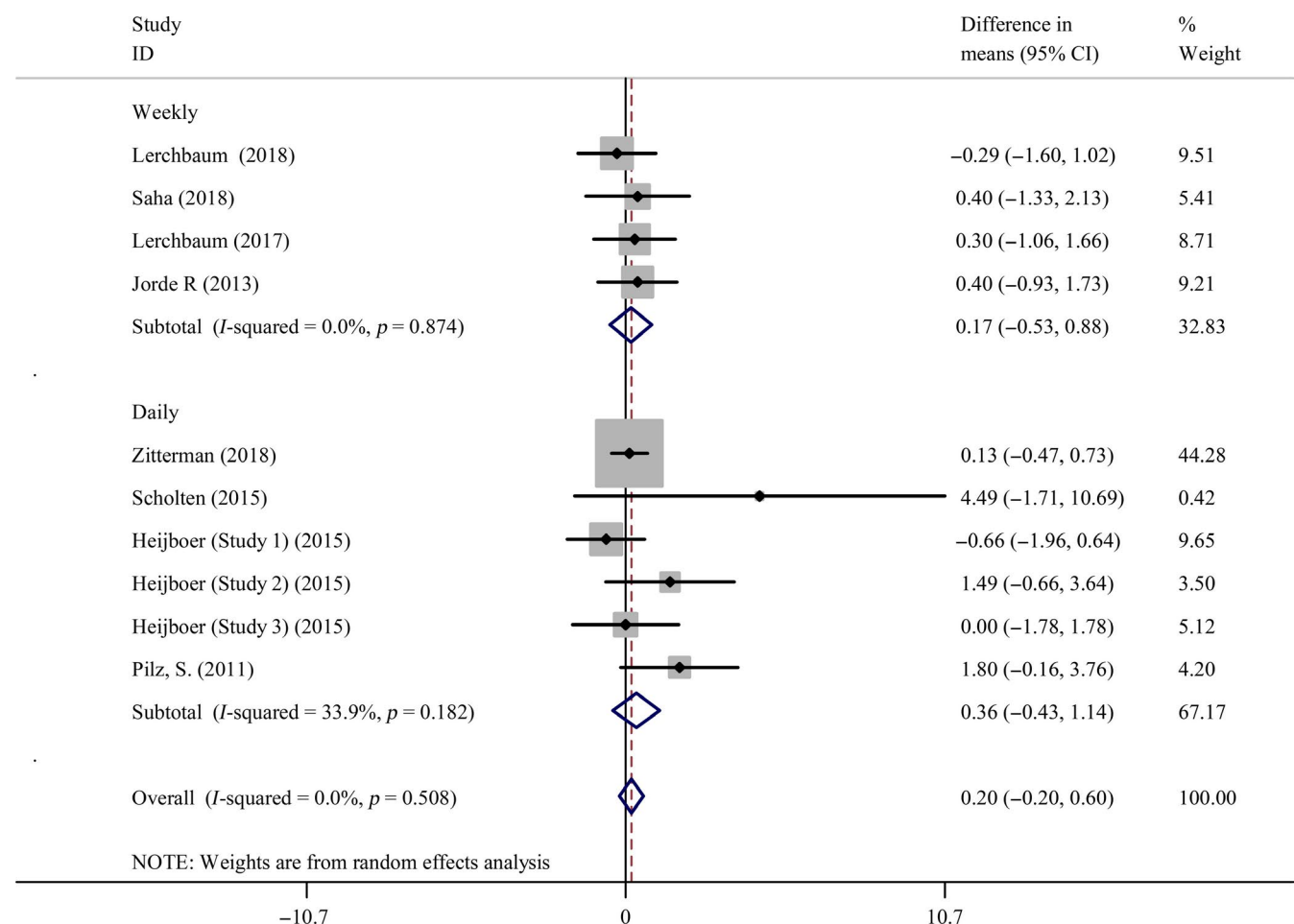


TABLE 1 Characteristics of randomised clinical trials included in the systematic review

First author	Country	Design	Study population	Mean age	Vitamin D (IU)	Kind of intervention	Kind of prescription	Duration of study (week)	outcome
Lerchbaum et al., (2017)	Austria	RCT	100 healthy men	39 ± 13	20,000 IU/week	Cholecalciferol	oral	12	TT,SHBG
Pilz, et al., (2011)	Germany	RCT	54 male patients	49.4 ± 10.2	3,332 IU/d	Cholecalciferol	oral	48	TT,SHBG
Saha et al., (2018)	India	Two-by-two factorial RCT	180 young Males	20.2 ± 2.2	60,000 IU/week	Cholecalciferol	oral	8	TT,SHBG
Scholten, et al., (2015)	USA	Two-by-two factorial RCT	40 physically active males	32.8 ± 1.7	4,000 IU/d	Cholecalciferol	oral	8	TT
Zittermann et al., (2018)	Germany	RCT	patients with Chronic heart failure	55.0 ± 9.9	4000 IU/d	Cholecalciferol	oral	144	TT,SHBG
Heijboer et al., (2015)	the Netherlands	RCT	92 male patients with Chronic heart failure	64.0 ± 9.0	2,000 IU/d	Cholecalciferol	oral	6	TT
	the Netherlands	RCT	49 male nursing home residents	84.2 ± 6.2	600 IU/d	Cholecalciferol	oral	16	TT
	the Netherlands	RCT	42 male non-Western immigrants in the Netherlands	48.9 ± 10.32	1200 IU/d	Cholecalciferol	oral	16	TT
Jorde et al., (2013)	Norway	RCT	129 men with BMI 28–47 kg/m ²	48.9 ± 10.6	40,000 IU / wk, 20 000 IU per week. All subjects were given 500 mg calcium daily	Cholecalciferol	oral	48	TT,SHBG
	Norway	RCT	53 men with 30–75 years old	51.2 ± 10	40,000 IU/ per week	Cholecalciferol	oral	24	TT,SHBG
	Norway	RCT	100 men	53.0 ± 11.1	40,000 IU / per week	Cholecalciferol	oral	24	TT,SHBG
Lerchbaum et al., (2018)	Austria	RCT	94 men	47 ± 12	20,000 IU/ week	Cholecalciferol	oral	12	TT,SHBG

TABLE 2 Study quality and risk of bias assessment using Cochrane Collaboration's tool

First author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Score	Overall quality
Lerchbaum et al., (2017)	+	?	+	?	+	+	4	Good
Zittermann et al., (2018)	+	+	+	+	+	+	6	Good
Saha et al., (2018)	+	+	?	?	+	+	4	Good
Pilz et al., (2011)	+	?	?	?	+	+	3	Good
Scholten et al., (2015)	+	?	?	?	+	+	3	Good
Jorde et al., (2013)	?	?	?	?	+	+	2	Fair
	+	+	+	?	+	+	5	Good
	+	+	?	?	+	+	4	Good
Heijboer et al., 2015	+	+	?	?	+	+	4	Good
	+	?	+	?	+	+	4	Good
	+	?	+	?	+	+	4	Good
Lerchbaum et al., (2018)	+	?	+	?	+	+	4	Good

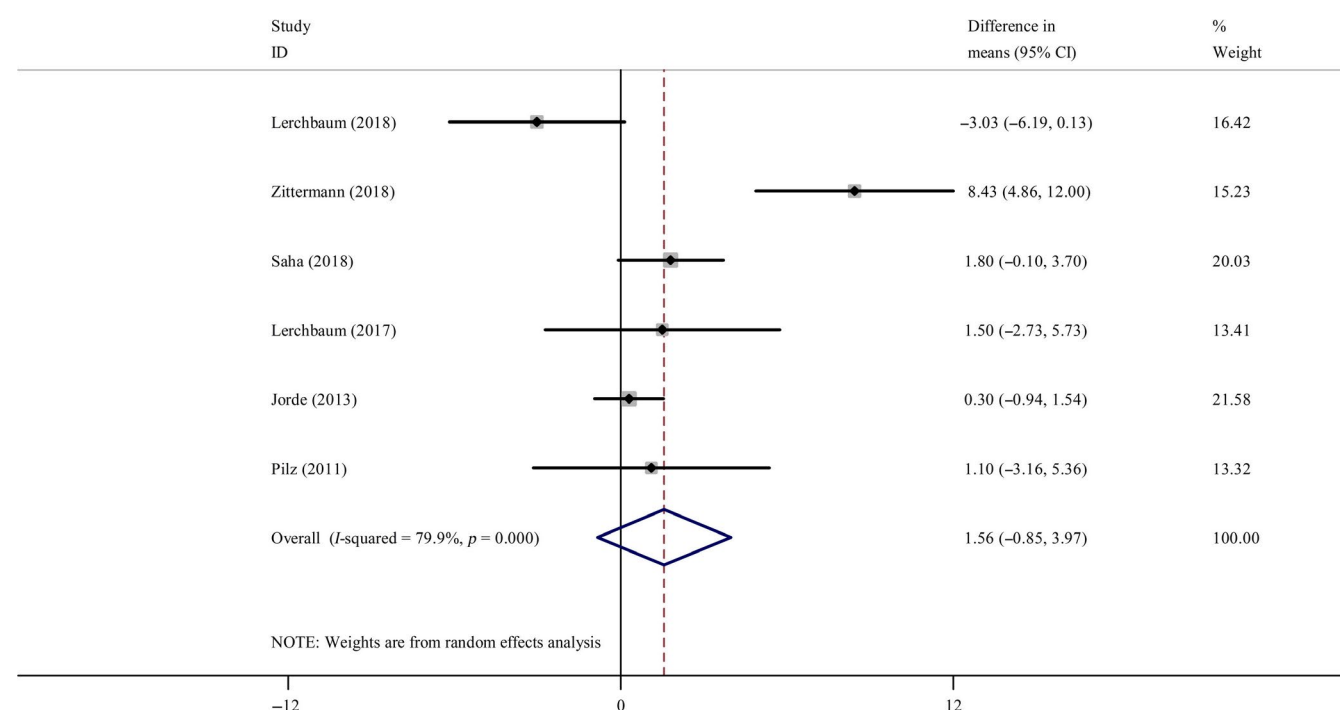
**FIGURE 2** Pooled Effect of vitamin D supplementation on TT forest plot

described random sequencing generation and only two studies were unclear in this regard (Lerchbaum et al., 2017; Lerchbaum et al., 2018). Allocation concealment and blinding of participants were performed in five studies. Outcome assessors were unclear

in most of the studies while all the studies had a low risk for incomplete outcome data and selective outcome reports. Most of the studies had scored three or more and only one study had fair quality.

TABLE 3 Subgroup analyses on the effect of vitamin D supplementation on total testosterone serum level

Study group	No. of effect sizes	Meta-analysis		Heterogeneity			
		Effect Mean difference (95%CI)	<i>p</i> Effect	Q statistic	<i>p</i> Within group	<i>I</i> ² (%)	<i>p</i> Between group
Type of vitamin D prescription							
Weekly	4	0.17 (−0.53, 0.88)	0.628	0.70	0.874	0.00	
Daily	6	0.36 (−0.43, 1.14)	0.372	7.56	0.182	33.9	
Duration							
Lower 16 weeks	5	−0.07 (−0.76, 0.62)	0.837	3.55	0.470	0.00	
16 weeks or higher	5	0.33 (−0.20, 0.60)	0.184	3.83	0.429	0.00	
Dose of vitamin D							
<3,000 IU/day	5	−0.04 (−0.70, 0.63)	0.916	3.20	0.525	0.00	
≥3,000 IU/day	5	0.38 (−0.20, 0.96)	0.195	4.32	0.364	7.40	
Baseline vitamin D level							
40 nmol/L or lower	5	0.14 (−0.40, 0.68)	0.615	4.32	0.364	7.40	
Higher than 40 nmol/L	5	0.34 (−0.38, 1.06)	0.355	3.37	0.444	0.00	
Baseline testosterone level							
13 nmol/L or lower	6	0.10 (−0.54, 0.73)	0.765	6.49	0.261	22.90	
Higher than 13 nmo/L	4	0.51 (−0.27, 1.30)	0.199	0.93	0.818	0.00	
Overall	10	0.20 (−0.20, 0.60)	0.336	8.26	0.508	0.00	–

**FIGURE 3** Pooled effect of vitamin D supplementation on SHBG forest plot

3.3 | Meta-analysis results

3.3.1 | Total testosterone

Change in TT concentration after vitamin D supplementation was assessed in eight studies containing 10 effect sizes with 1,061 participants (Heijboer et al., 2015; Jorde et al., 2013; Lerchbaum et al.,

2017; Lerchbaum et al., 2018; Pilz et al., 2011; Saha & Goswami, 2018; Scholten et al., 2015; Zittermann et al., 2018). The overall effect of meta-analysis showed no significant effect of vitamin D on TT (WMD = 0.20, 95% CI: −0.20, 0.60, *p* = 0.336), and heterogeneity (*I*² = 0.0%, *p* = 0.508) was not observed among the studies (Figure 2). According to subgroup analysis, supplementation with vitamin D was not significant when considering type of vitamin D

TABLE 4 Sensitive analyses on the effect of vitamin D supplementation on SHBG serum level

		MD (95% CI)	<i>p</i> Effect	Q statistic	<i>p</i> Heterogeneity	<i>I</i> ² (%)
SHBG mean difference	Before omitting Zitterman study	1.56 (−0.85, 3.97)	0.204	24.87	0.0001	79.90
	After omitting Zitterman study	0.40 (−1.08, 1.88)	0.597	6.97	0.137	42.6

Abbreviations: CI, confidence interval; MD, mean differences; SHBG, sex hormone-binding globulin

prescription (weekly: WMD = 0.17, 95% CI: −0.53, 0.88, *p* = 0.874; daily: WMD = 0.36, 95% CI: −0.43, 1.14, *p* = 0.182), duration of vitamin D (Lower 16 weeks: WMD = −0.07, 95% CI: −0.77, 0.62, *p* = 0.470; 16 weeks or higher: WMD: 0.33, 95% CI: −0.16, 0.83, *p* = 0.429), different type of vitamin D dose ($\geq 3,000$ IU/day: WMD: 0.38, 95% CI: −0.20, 0.96, *p* = 0.364; $< 3,000$ IU/day: WMD: −0.04, 95% CI: −0.70, 0.63, *p* = 0.525), baseline 25(OH)D level (40 nmol/L or lower: WMD: 0.14, 95% CI: −0.40, 0.68, *p* = 0.364; higher than 40 nmol/L: WMD: 0.34, 95% CI: −0.38, 1.06, *p* = 0.444) or baseline TT level (13 nmol/L or lower: WMD: 0.10, 95% CI: −0.54, 0.73, *p* = 0.261; higher than 13 nmol/L: WMD: 0.51, 95% CI: −0.27, 1.29; Table 3).

3.3.2 | Sex hormone-binding globulin

Six studies with 843 participants (Lerchbaum et al., 2017; Jorde et al., 2013; Lerchbaum et al., 2018; Pilz et al., 2011; Saha & Goswami, 2018; Zittermann et al., 2018) were considered for assessing the effect of vitamin D supplementation on SHBG. The overall results showed no significant effect of vitamin D on SHBG (MD = 1.56, 95% CI: −0.85–3.97, *p* = 0.204), although with substantial heterogeneity (*I*² = 79.90%, *p* = 0.000; Figure 3).

3.3.3 | Sensitivity analysis and publication bias

Heterogeneity was observed in the selected studies, considering the effect of vitamin D on SHBG (*I*² = 79.90%; *p* heterogeneity = 0.000). Given the high vitamin D3 dose (4,000 IU daily) for 3 years in Zittermann et al.'s study (Zittermann et al., 2018) in comparison with another study, the sensitive analysis was performed by examining the impact of one trial on the overall effect. When the trial of Zittermann et al. was removed, heterogeneity plummeted (*I*² = 42.6%; *p* heterogeneity = 0.137; Table 4), suggesting that this trial was the main source of heterogeneity in SHBG.

There was no evidence of a publication bias for the effect of vitamin D on TT (Egger's test, *p* = 0.602) and SHBG (Egger's test, *p* = 0.806).

NutriGrade

The overall credibility of evidence for the effect of vitamin D supplementation on TT and SHBG level was scored "Moderate," meaning that there was a modest assurance in the effect size. Additional evidence is likely to change the effect estimate.

4 | DISCUSSION

In this systematic review and meta-analysis of RCTs, vitamin D supplementation had no significant effect on TT and SHBG in men. In

term of intervention, treatment duration (< 16 or ≥ 16 weeks), type of prescription (weekly or daily), daily doses of vitamin D supplementation ($< 3,000$ IU/day or $\geq 3,000$ IU/day) and baseline 25(OH) D and TT levels confirmed the null finding in total analysis. Our results are consistent with the current systematic review (Trummer et al., 2018), which found conflicting results about the effect of vitamin D supplementation on TT in men in RCTs and observational studies. The most observational studies in this systematic review found an independent association between vitamin D and TT. Similarly, Nimptsch and coworkers (Nimptsch, Platz, Willett, & Giovannucci, 2012) showed an independent association between 25 (OH) D with TT and FT in 1,362 men. However, in Wang et al.'s study (Wang et al., 2015), positively correlated between lower levels 25(OH)D and high prevalence of hypogonadism, was found in Chinese men. The discrepancy in these observational studies included in the current systematic review could be related to the type of intervention design, age, sample size and statistical methods used for analysis. Although RCTs studies about the effect of vitamin D supplementation on TT are limited, two out of seven intervention studies the mentioned review revealed a positive effect of vitamin D on TT (Canguven, Talib, Ansari, Yassin, & Al Naimi, 2017; Pilz et al., 2011). Pilz et al., (Pilz et al., 2011) reported a beneficial effect on increasing TT by vitamin D supplementation (3,332 IU daily) for one year. The difference may be explained by the subjects who were healthy men with 25(OH) D < 50 nmol/L and TT in the low level of normal range (9.09–55.28 nmol/L). Noteworthy between group's analyses was not performed in this study. On the other hand, lack of control group in Canguven's study might cause different result.

In another meta-analysis (Azadi-Yazdi, Nadjarzadeh, Khosravi-Boroujeni, & Salehi-Abargouei, 2017), which was performed on PCOS women, vitamin D supplementation had a positive effect on TT, whereas no effect was observed on free testosterone and SHBG. In this meta-analysis, the significant effect of vitamin D on TT was shown only in uncontrolled before/after trials.

There is biological evidence that supports the effect of vitamin D on TT in men. Vitamin D and vitamin D receptors are expressed in various parts of the male reproductive system, including Leydig cells, indicating that vitamin D is involved in the regulation of testis (Blomberg Jensen, 2014). The presence of vitamin D metabolising enzymes in different parts of the male reproductive system suggests that vitamin D plays a role in local regulation in addition to paracrine action (de Angelis et al., 2017). Increasing testosterone in rats after two- and fivefold injection of 1α and 25dihydroxy vitamin D indicates that vitamin D indirectly affects target tissue through excess calcium (Sonnenberg et al., 1986). Vitamin D can mediate the effect

of testosterone through osteocalcin production which is secreted by osteoblast. It has been hypothesised that osteocalcin might have an indirect role in stimulating testosterone production in the testis (de Angelis et al., 2017). Despite these evidences in which based on in vivo and animal studies, contradict results of our study may be related to subject with high baseline 25(OH) D levels, so we could not investigate the effect of vitamin D in men with severe vitamin D deficiency. Furthermore, due to high baseline TT level, the effect of vitamin D was not observed in hypogonadism men or men with low normal TT. In summary, there is only one study with duration more than one year, and it is assumed that longer duration of vitamin D supplementation might increase androgen level in men. Another reason may be related to participants with different characters in studies such as subjects with significant weight loss in Pilz et al.'s study, chronic heart failure patients in Heijboer et al.'s study [28] and athletes in Scholten et al.'s study (Scholten et al., 2015). High level of testosterone in athletes may be a reason for the limited increase in testosterone concentration after vitamin D supplementation in Scholten et al.'s study.

To our knowledge, this is a first systematic and meta-analysis review that summarised RCTs to discover the role of vitamin D in androgen in men. The primary point of this study was that gender effect was lost, given that all the participants were male. An additional strength was that all the participants were in middle age and baseline 25(OH)D < 75. Furthermore, lack of heterogeneity among the included studies in TT increased the reliability of our results.

Although this study provided that vitamin D supplementation did not significantly affect TT and SHBG, the reader should note its limitations and ways in which future research could be enhanced. Firstly, despite our attempt to find all the literature conducted on this issue, there were studies with unavailable full text. Secondly, because of the limited number of studies on SHBG, the power of analysis was reduced. Thirdly, since the high prevalence of TT and vitamin D deficiency was not considered among the patients, we could not examine the effect of vitamin D supplementation in hypogonadism in men with severe vitamin D deficiency. On the other hand, the dose used in the studies, as well as the duration of intervention, varied from study to study, which could affect the reported outcome. Finally, although seasonal changes play a vital role in the synthesis of vitamin D, our selected studies did not consider the effect of this confounder.

5 | CONCLUSION

This paper presented outcomes that investigated the effect of vitamin D supplementation on androgen levels in men. The main outcome of this study reaffirmed the null effect of vitamin D supplementation on TT and SHBG in men. To solve this problem in the future, we recommend further studies that consider the effect of vitamin D over a longer period in men with hypogonadism and severe vitamin D deficiency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

AN and MM designed the search and performed the literature search. EHM and MM screened all articles and extracted information from the included articles. AG and EHM assessed the risk of bias and MM implemented the related analysis. EHM wrote the manuscript. Ultimately, all the authors read and confirmed the final manuscript.

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