International Journal of Surgery 71 (2019) 101–109

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

The association between serum vitamin D, fertility and semen quality: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Vitamin D
Male fertility
Semen quality
Systematic review
Meta-analysis

ABSTRACT

Purpose: A number of studies have examined the association between vitamin D, fertility and semen quality, however, findings have been inconclusive. Herein, we systematically reviewed available observational studies to elucidate the overall relationship between vitamin D, fertility and semen quality in adult population.

Methods: PubMed, Cochrane's Library, Science Direct, Scopus, Google Scholar and ISI Web of Science databases were searched until December 2018 for all available studies evaluating the association between vitamin D, fertility and semen quality. The Newcastle-Ottawa Quality Assessment Scale was used to examine the quality of each study.

Results: A total of 18 studies out of 1843 met our inclusion criteria and were included in our systematic review and meta-analysis. Serum 25(OH)D3 was significantly higher in fertile subjects compared to infertile ones (WMD -0.63; 95% CI, −1.06 to −0.21; P = 0.003). Furthermore, there was a significant association between serum 25(OH)D, sperm motility (WMD -5.84; 95% CI, −10.29 to −1.39; P = 0.01) and sperm progressive motility (WMD -5.24; 95% CI, −8.71 to −1.76; P = 0.003).

Conclusion: Our findings add to the existing literature supporting the concept that nutrition, especially vitamin D, plays an important role in men's sexual health. It should be noted that because of significant heterogeneity among the included studies, caution is warranted when interpreting the results. Further well-designed prospective cohort studies and clinical trials are needed for better understanding of the relationship between vitamin D and fertility and its components.

1. Introduction

Human infertility affects 10–15% of couples and is characterized as a couple's inability to conceive for 12 months. The rate of male infertility arises alongside with female infertility which makes it a worldwide concern and contributes to the problem in approximately 50% of infertility cases [1,2]. Male fertility potential is clinically examined by semen analysis. There are a wide range of macro and micronutrients such as galactose, fructose, amino acids, zinc, potassium, magnesium, and vitamin C which form the components of semen. Semen quality and its ability to fertilize the female ovule is dependent on important factors including quality and quantity of the sperm [3].

Although semen quality is mostly determined by demographic factors (age) and lifestyle indices (BMI, smoking and alcohol), nutritional elements have been indicated as having crucial role in sperm quality modification as well [4–7]. These include zinc [8,9], selenium [10], carnitine [11], CoQ10 [12], omega-3 [13] and various antioxidants [14] proven to be associated with semen quality. In addition, vitamin D (Vit D) has gained major attention in recent years in this regard with a role that goes beyond calcium homeostasis and bone health. Body of evidence is increasing regarding the functions of vit D in health and disease conditions through modulating the immune and cardiovascular factors. Also, there are reports of vitamin D regulatory effects on the proliferation and differentiation of benign and malignant tissues [15-17]. Finally, because of the significant effects of this nutrient on the spermatogenesis and maturation of sperm cells, it could be conjectured that vit D might influence semen quality.

However, increasing body of literature have shown paradoxical relationships between vit D and semen quality with some studies suggesting a significant association between serum vit D level and semen

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https://doi.org/10.1016/j.ijsu.2019.09.025
Received 11 June 2019; Received in revised form 6 September 2019; Accepted 19 September 2019
Available online 24 September 2019
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quality parameters [18,19] while, others did not support such an association [20,21]. Currently, there is insufficient evidence showing whether serum vit D is related to semen quality, and the determination of this relationship has rarely been conducted. To address these issues, we carried out this systematic review and meta-analysis by pooling the results from observational studies to examine two topics among adult population: First, the possible association between serum vit D and parameters of semen quality. Second, to compare the serum levels of vit D in fertile and infertile subjects. Findings will be used to inform public health programming and improve diet quality among men with infertility problems.

2. Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, Assessing the methodological quality of systematic reviews (AMSTAR) Guidelines and was registered on Prospero database (CRD42019123355) [22].

2.1. Data source and search strategy

We searched databases including PubMed, Scopus, Cochrane Library, Science direct and ISI databases up to December 2018 to identify relevant studies. The reference lists of the included articles were also screened to identify additional eligible studies. The following search strategy was run in PubMed and tailored to each database when necessary: “vitamin D″ OR “25-Hydroxyvitamin D” OR “cholecalciferol” OR “ergocalciferol” OR “calcitriol” AND “fertility” OR “infertility” OR “male fertility” OR “male infertility” OR “sperm dysfunction” OR “varicocele” OR “asthenozoospermia” OR “oligozoospermia” OR “oligoasthenozoospermia” OR “oligoasthenoteratozoospermia” OR “teratozoospermia” OR “semen quality” OR “sperm quality” OR “semen volume” OR “sperm count” OR “sperm concentration” OR “sperm motility” OR “sperm morphology” OR “sperm motion”.

2.2. Inclusion criteria

Articles were considered for inclusion if they (I) were observational in design; (II) evaluated the association between vit D and semen quality or fertility/infertility; and (III) assessed and reported means, medians or odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the following outcomes: sperm motility, progressive motility, morphology, volume, concentration and sperm count. Articles were excluded if they were of non-human design, review articles, case reports, editorials, poster abstracts or without original data or that did not report relevant outcome data.

2.3. Data extraction

For each study, the following information was extracted: first author's name, year of publication, country, sample size, participants' age, gender and health status, study design, dietary assessment method, covariates used in adjustments and reported semen indices. The process of data extraction and assessment of study quality was conducted by two independent reviewers. Any discrepancies in terms of the decision on a given study were dealt with via discussion and if necessary, arbitration by a third reviewer.

2.4. Study quality

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of each study [23]. The scale consists of assessment of three domains: selection (5 points), comparability (2 points) and outcome (3 points) for a total score of 10 points. Studies scoring 7–10, 3–6 and 0–3 points were identified as high, moderate and low quality, respectively [24].

2.5. Statistical analysis

We conducted a meta-analysis to provide quantitative summary estimates of the association between vit D and semen quality parameters including volume, count, concentration, motility, progressive motility and morphology, and also to compare vit D status among fertile/infertile male subjects. Meta-analysis was performed using weighted mean difference (WMD) with 95% confidence intervals (CIs) with random effect model. The sensitivity analyses were also performed to assess the influence of each individual study on the stability of the meta-analysis results. Each time one study was excluded to show that study's impact on the combined effect estimate. We also conducted subgroup analyses based on the different quality of studies or studies' location. Statistical analyses were carried out using Stata, version 11.2 (Stata Corp, College Station, TX, USA). P-values less than 0.05 were considered statistically significant. The I^2 index was evaluated to assess heterogeneity. Low, moderate and high heterogeneity were defined as I^2 index equal to 25, 50 and 75%, respectively [25]. Publication bias was assessed by visual inspection of the funnel plots and Egger's and Begg's tests were conducted to determine the degree of funnel plot asymmetry with $p < 0.05$ representing significant publication bias [21].

3. Results

3.1. Search results

Our preliminary search through databases yielded a total of 1843 articles. After removing duplicates, 1064 remaining articles were reviewed based on title and abstracts by two independent reviewers. Fifty-nine papers were retrieved and reviewed based on full text and finally 18 articles met the inclusion criteria and were included in our systematic review and meta-analysis. The PRISMA flow diagram summarizes the results of the study selection process for this systematic review and meta-analysis (Fig. 1).

3.2. Overview of included studies

A total of 18 studies involving 4773 participants were included in this systematic review and meta-analysis. The included observational studies were conducted between 2011 and 2018. Among included studies, 5 were from Denmark [26–30], 3 from Italy [31–33], 2 from Iran [34,35], 2 from China [36,37] and others were established from Poland [38], United states [39], Turkey [40], Jordan [41], Pakistan [42] and Iraq [43]. Among included observational studies, 13 were cross-sectional in design [26,27,29–34,37–40,44] and 5 were case controls [28,35,41–43]. Only 2 studies [34,39] examined dietary intakes of the participants, and others did not mention anything [26–33,35,37–41,43,44]. Four of the included studies recruited fertile participants [26,29,38,39], 5 were conducted on sub-fertile individuals [27,30,32,34,40] and others used both fertile and infertile subjects [28,31,33,35,37,41–44]. Based on the NOS, 13 studies ranked as high quality [26–30,33–35,37–39,41,44] and 5 had moderate quality [31,32,40,42,43]. Characteristics of the included studies are illustrated in Table 1.

3.3. Findings from meta-analysis

3.3.1. The association between serum 25(OH)D level and fertility

Nine studies with 2008 participants examined the association between serum 25(OH)D and fertility among 1157 infertile and 851 fertile individuals [28,31,34,37,40–44]. There was no significant association between serum 25(OH)D and fertility status (WMD -6.48; 95% CI, −13.60 to 0.64; P = 0.075). There was evidence of heterogeneity

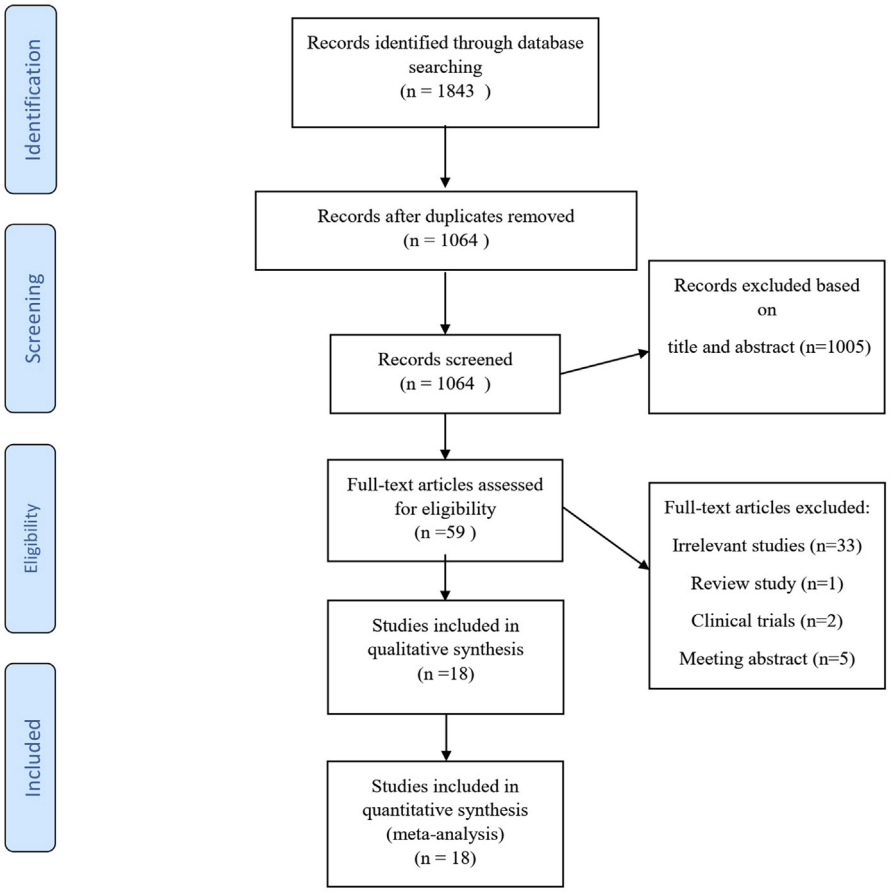

Fig. 1. The flow diagram of study selection.

between the effect sizes of the included studies (I^2 = 99.7% p < 0.001). So, we calculated subgroup analysis based on the studies' quality (high-quality quality vs moderate). There was significant association between serum 25(OH)D and fertility status in both moderate quality studies (WMD -13.73; 95% CI, −24.86 to −2.61; P = 0.016), with significant heterogeneity (I^2 = 99.2% p < 0.001), and high-quality studies (WMD -0.63; 95% CI, −1.06 to −0.21; P = 0.003), without any evidence of significant heterogeneity (I^2 = 0.0% p = 0.619). Furthermore, there was evidence of significant between sub-group heterogeneity (P < 0.001) which explains our results among subgroup. In other words, vit D was significantly higher in fertile subjects compared to infertile ones. No evidence of publication bias was found (Begg's test: P = 0.095, Egger's test: P = 0.970) (Fig. 2).

3.3.2. The association between serum 25(OH)D level and semen volume

Five studies with 1106 participants examined the association between serum 25(OH)D and semen volume [26,27,29,33,34]. There was no significant association between serum 25(OH)D and semen volume (WMD 0.08; 95% CI, −0.10 to 0.26; P = 0.372) with no evidence of heterogeneity between the effect sizes of the included studies (I^2 = 0.0% p = 0.692). No evidence of publication bias was observed (Begg's test: P = 0.327, Egger's test: P = 0.707) (Fig. 3).

3.3.3. The association between serum 25(OH)D level and sperm concentration

Nine studies with 1405 participants examined the association between serum 25(OH)D and sperm concentration [26,27,29,32–35,39,41]. There was no significant association between serum 25(OH)D and sperm concentration (WMD -0.13; 95% CI, −2.79 to 2.53; P = 0.925). There was no evidence of heterogeneity between the effect sizes of the included studies (I^2 = 0.0% p = 0.665). No evidence of publication bias was found (Begg's test: P = 0.211, Egger's test: P = 0.132) (Fig. 4).

3.3.4. The association between serum 25(OH)D level and sperm count

Four studies with 936 participants examined the association between serum 25(OH)D and sperm count [26,27,29,39]. There was no significant association between serum 25(OH)D and sperm concentration (WMD -4.17; 95% CI, −16.83 to 8.49; P = 0.518). There was evidence of heterogeneity between the effect sizes of the included studies (I^2 = 72.5% p = 0.012). No evidence of publication bias was found (Begg's test: P = 0.497, Egger's test: P = 0.661) (Fig. 5).

3.3.5. The association between serum 25(OH)D level and normal sperm morphology

Nine studies with 1405 participants examined the association between serum 25(OH)D and normal sperm morphology [26,27,29,32–35,39,41]. There was no significant association between serum 25(OH)D and sperm concentration (WMD -0.01; 95% CI, −0.44 to 0.41; P = 0.951). There was no evidence of heterogeneity between the effect sizes of the included studies (I^2 = 32.3% p = 0.160). No evidence of publication bias was found (Begg's test: P = 0.677, Egger's test: P = 0.865) (Fig. 6).

3.3.6. The association between serum 25(OH)D level and sperm motility

Seven studies with 1212 participants examined the association between serum 25(OH)D and sperm motility [26,27,29,33,34,39,41]. There was a significant association between serum 25(OH)D and sperm motility (WMD -5.84; 95% CI, −10.29 to −1.39; P = 0.01). There was evidence of heterogeneity between the effect sizes of the included studies (I^2 = 84% p < 0.001), Therefore, we did sub-group analysis based on the quality of the studies, status of the recruited participants

Table 1
Characteristics of included studies.

Author, Year	Location	Sample size	Age (Mean ± SD)	Study Design	Men's health status	DAM	Adjusted variables	Quality assessment score
Ramlau-Hansen et al., 2011	Denmark	307	18–21	Cross-sectional	Fertile	–	Season, history of diseases of the reproductive organs, smoking, maternal smoking during pregnancy, maternal alcohol during pregnancy, abstinence time, spillage during collection of the sample.	8/10
Blomberg Jensen et al., 2011	Denmark	300	18–21	Cross-sectional	Fertile	–	Duration of abstinence, season and medication, fever, time from ejaculation to motility assessment	9/10
Jozkow et al., 2018	Poland	177	20–35	Cross-sectional	Fertile	–	Smoking, alcohol consumption, carrying a telephone in a pants pockets, BMI, WHR, caffeine consumption and physical activity	8/10
Hammoud et al., 2012	USA	170	> 18	Cross-sectional	Fertile	Dietary questionnaire	Age, BMI, season, alcohol intake and smoking	8/10
Akhavizadegan et al., 2017	Iran	103	30 ± 5	Case control	Fertile and infertile	–	–	6/9
Abbasihormozi et al., 2016	Iran	278	20–50	Cross-sectional	Sub-fertile	FFQ	Age, season, and BMI	9/10
Tartagni et al., 2015	Italy	102	35.3 ± 2.6	Cross-sectional	Sub-fertile	–	–	6/10
Blomberg Jensen et al., 2016	Denmark	1189	28–38	Cross-sectional	Sub-fertile	–	Age, BMI and < !–Soft-enter Run-on– > smoking	10/10
Tirabassi et al., 2016	Italy	104	33.1 ± 4.78	Cross-sectional	Fertile and infertile	–	Age, BMI, PTH, and varicocele	8/10
Rehman et al., 2018	Denmark	313	25–55	Cross-sectional	Sub-fertile	–	–	8/10
Ozdemir et al., 2015	Turkey	198	30.8 ± 5.4	Cross-sectional	Sub-fertile	–	–	6/10
Zhu et al., 2016	China	265	28.10 ± 0.57	Cross-sectional	Fertile and infertile	–	–	7/10
Alzoubi et al., 2017	Jordan	117	29.20 ± 1.15	Case control	Fertile and infertile	–	–	6/9
Hussain et al., 2018	Pakistan	275	25–70	Case control	Fertile and infertile	–	–	5/9
Yang et al., 2012	China	559	20–40	Cross-sectional	Fertile and infertile	–	–	7/10
Foresta et al., 2011	Italy	98	35.83 ± 5.83	Cross-sectional	Fertile and infertile	–	–	5/10
Albaldawy et al., 2017	Iraq	88	33 ± 1.24	Case control	Fertile and infertile	–	–	4/9
Blomberg Jensen et al., 2012	Denmark	130	18–45	Case control	Fertile and infertile	–	–	6/9

DAM: Dietary assessments method, FFQ: Food frequency questionnaire, BMI: Body Mass Index, WHR: Waist to hip ratio, PTH: Parathyroid hormone.

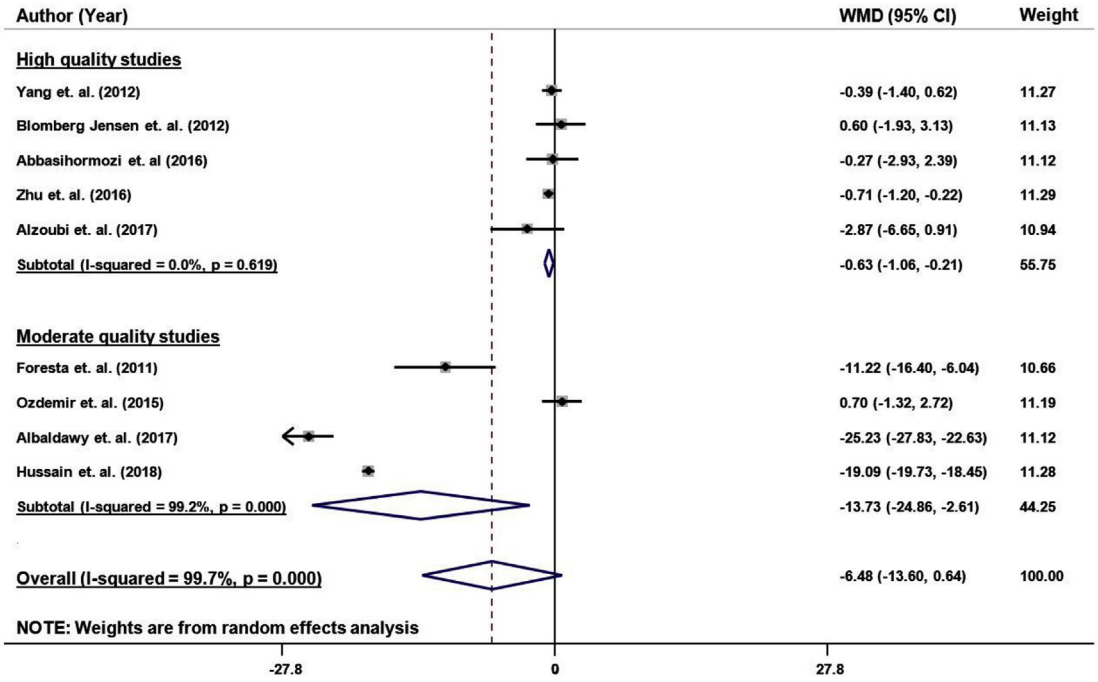

Fig. 2. Forest plot of the association between serum 25(OH)D level and fertility.

and studies' location. However, the heterogeneity did not decline. No evidence of publication bias was found (Begg's test: P = 0.881, Egger's test: P = 0.583) (Fig. 7).

3.3.7. The association between serum 25(OH)D level and sperm progressive motility

Eight studies with 1201 participants examined the association between serum 25(OH)D and sperm progressive motility [26,27,29,33,34,39,41]. There was no significant association between serum 25(OH)D and sperm progressive motility (WMD -2.57; 95% CI, −6.53 to 1.39; P = 0.01). There was evidence of heterogeneity between the effect sizes of the included studies (I^2 = 90.6% p < 0.001). As a result, sub-group analysis was done based on quality of the studies (high vs moderate quality). There was a significant association in the sub-group of high quality studies (WMD -5.24; 95% CI, −8.71 to −1.76; P = 0.003) and heterogeneity declined significantly (I^2 = 54% p = 0.069). No evidence of publication bias was found (Begg's test: P = 0.322, Egger's test: P = 0.512) (Fig. 8).

4. Discussion

To the best of our knowledge, this is the first attempt to perform a systematic review and meta-analysis regarding the relationship between vit D, fertility and semen quality parameters. All the observational studies assessing this link were collected. We found that serum vit D is significantly lower in infertile individuals compared to the fertile ones which is consistent with previous reports [31,42,43].

Our analysis also revealed that vit D is significantly associated with sperm motility and progressive motility, but not other sperm parameters, which is in line with some previous reports [26,27,45] and inconsistent with others [39,45]. These discrepancies should be interpreted with caution. It is possible that the association between vit D and semen quality parameters, reported in rodent studies, do not apply to humans or these associations may have only been reflected in severe vit

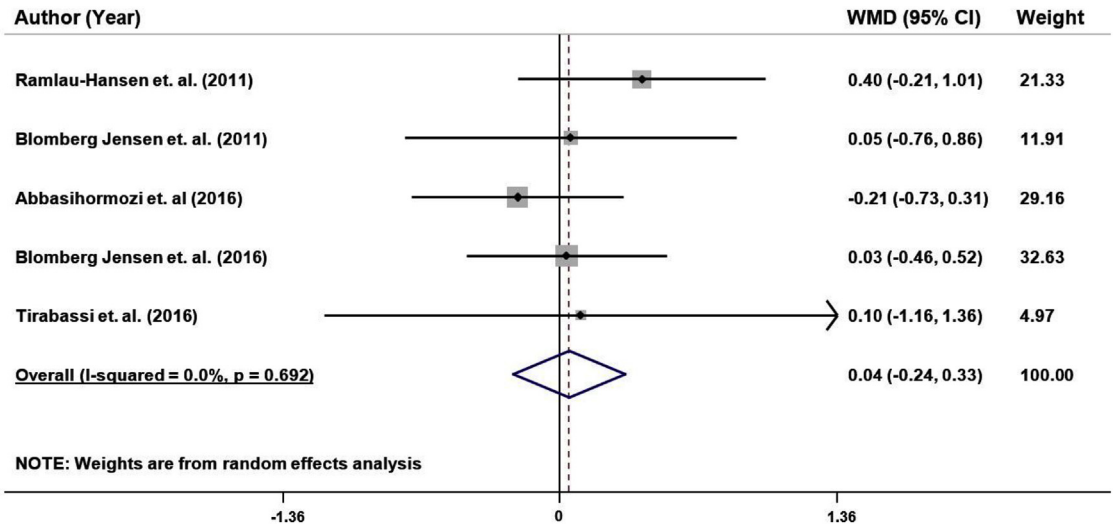

Fig. 3. Forest plot of the association between serum 25(OH)D level and semen volume.

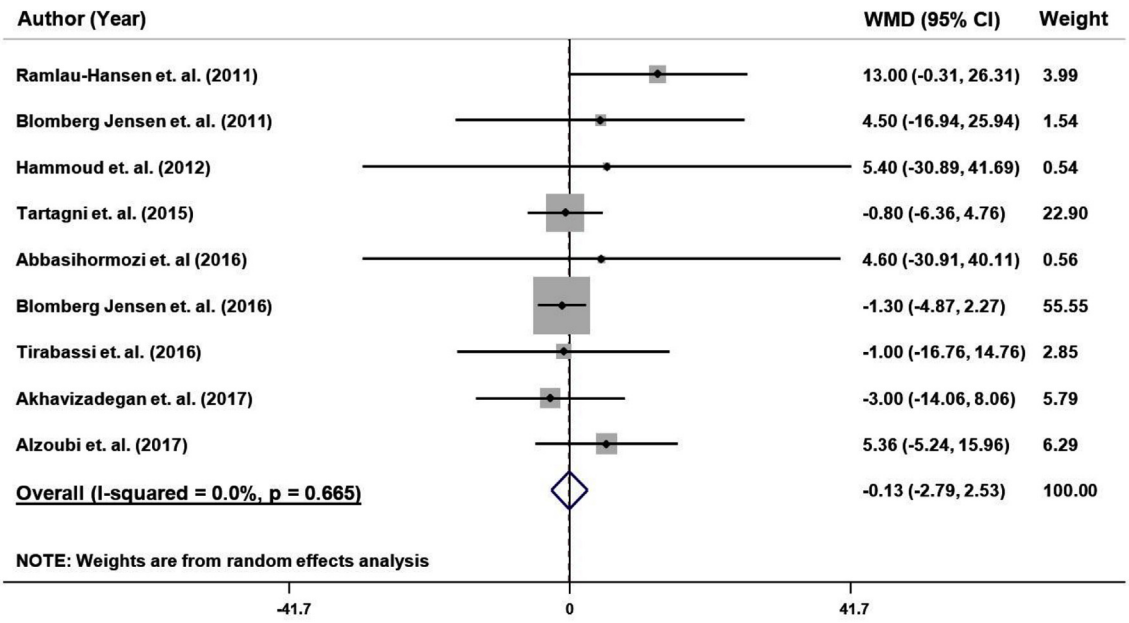

Fig. 4. Forest plot of the association between serum 25(OH)D level and sperm concentration.

D deficiency [45]. Furthermore, exposure data meaning serum vit D was not taken at the time of spermatogenesis that is up to 72 days before sampling of fertility markers [45]. Moreover, residual confounding or confounding from unknown factors could negatively affect the association between vit D and semen quality parameters [45]. Furthermore, it should be mentioned that serum vit D level has a relatively short half-life which could be another explanation for these inconsistencies [46]. In addition, previous reports have suggested an inverted 'U Shaped' relation of semen quality parameters to vit D which should be taken into account when interpreting the results [26,47]. Additionally, presence of heterogeneity between studies could be another explanation for these inconsistent findings. Also, there are substantial inter-assay differences in performance of commercially available kits for serum vit D assay [48]. Moreover, sperm parameters vary greatly over time [49]. Besides, there are some other factors that may be related to semen quality parameters including age, BMI, varicocele, lifestyle and dietary habit which were not controlled in all of the included studies.

Recently, Vit D and its role in the pathogenesis of infertility and impaired semen quality has been examined in various studies. These have shed a light on the association between vit D, male infertility and related mechanisms [26,27,34,39]. Vit D is a fat-soluble micronutrient with its major natural source being in the synthesis of cholecalciferol in the skin from cholesterol through a chemical reaction that is dependent on sun exposure [50]. Previously, vit D has been known for its roles in calcium/phosphate homeostasis, cardiovascular and bone health, immune system and carcinogenesis [51]. Since 1979, an increasing body of evidence indicates that vit D also affects male reproduction. Vit D could exert its physiological effects through VDR (vitamin D receptor) abundant in the reproductive system including spermatozoa [52,53]. Vit D is metabolized locally in the male reproductive tract and the concentrations of its active form, 1, 25(OH)2D3which has induced an effect in the in vitro studies, are close to the physiological concentrations in serum ($\approx 1 \times 10^{-10}$ M) [54]. Presence of VDR and vit D metabolizing enzymes in the neck of mature spermatozoa indicates that vit D may have a function in the reproductive tract [26]. Vit D supplementation successfully rehabilitated fertility in male and female rats previously fed on a diet depleted of vit D. Also, calcium supplementation without correction of vit D status restored fertility, suggesting that vit D could improve fertility status through calcium-related mechanism

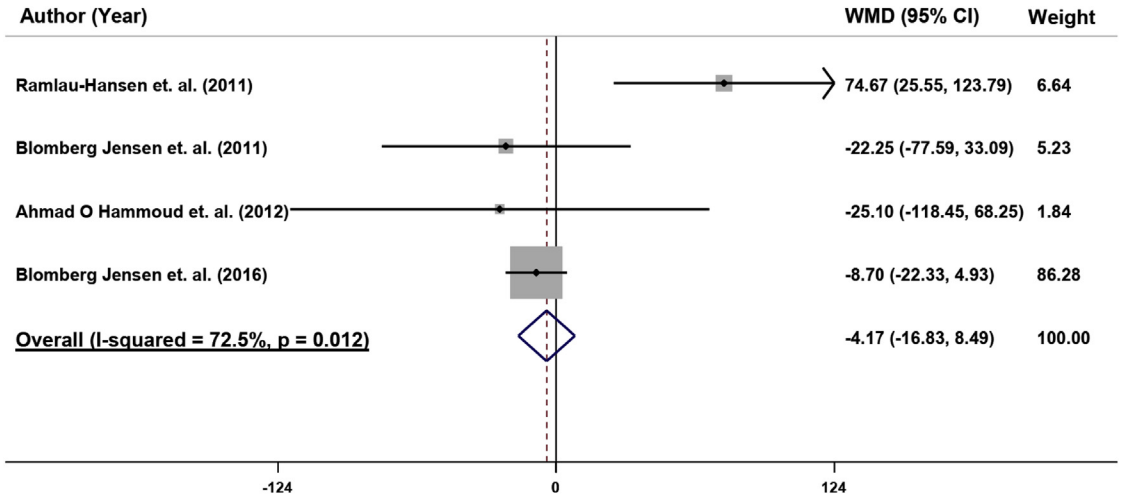

Fig. 5. Forest plot of the association between serum 25(OH)D level and sperm count.

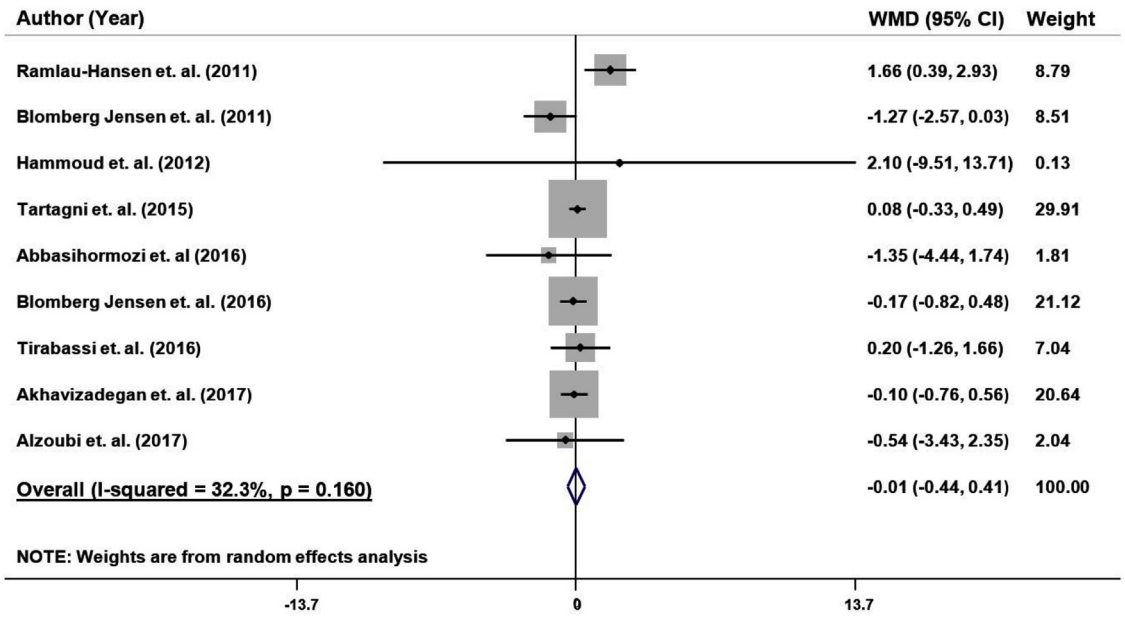

Fig. 6. Forest plot of the association between serum 25(OH)D level and sperm morphology.

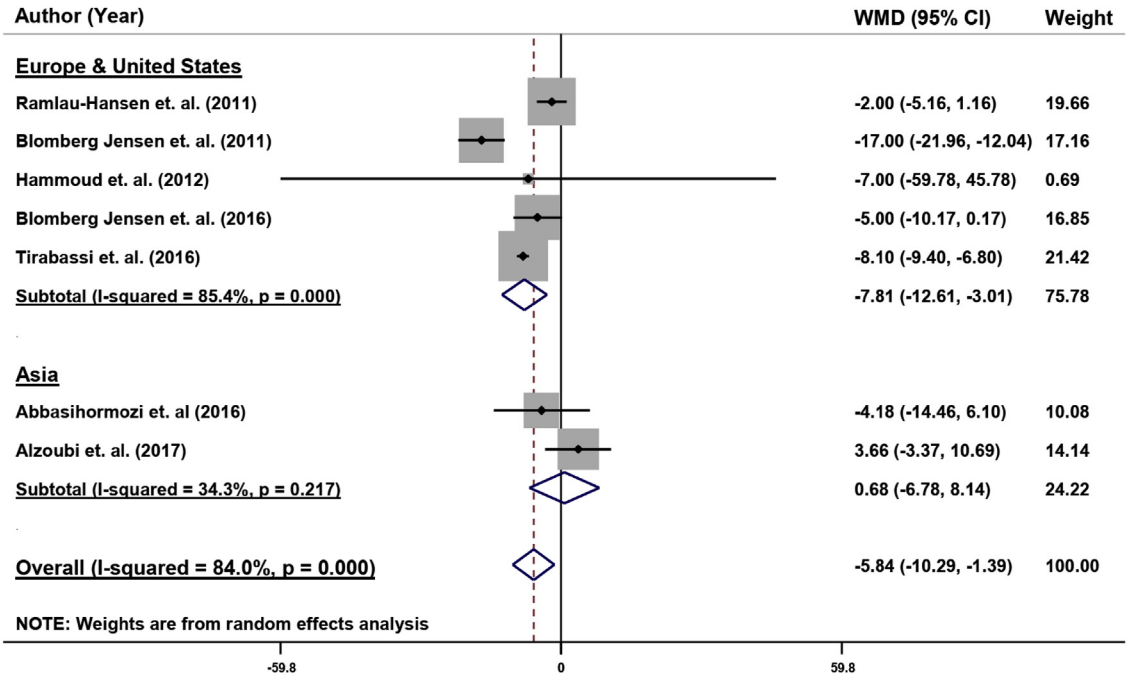

Fig. 7. Forest plot of the association between serum 25(OH)D level and sperm motility.

[24,55]. Further studies revealed that vit D could increase content of calcium in the neck and head of spermatozoa, which might be a probable link between vit D and sperm motility and also, acrosin activity [56]. Furthermore, vitamin D directly affects germ cells and the cells lining the reproductive tract [38].

The present study has some limitations that warrant consideration. First, significant heterogeneity was present in our analysis that could limit the generalization of our findings. Heterogeneity between the studies may be explained by the number of participants, participants' different serum vit D levels, adjusted models, different study populations and ethnicity. Moreover, the nature of cross-sectional studies makes it impossible to draw a causal link between variables. Since, it is a snapshot of the population, it could be altered overtime and include Neyman's bias (prevalence-incidence bias), which is another form of selection bias and highlighted in longer-lasting disorders [57]. Moreover, studies did not consider seasonal variation in serum vit D level. Another limitation which certainly affects the results is in case of vit D binding protein concentrations and vitamin D receptor's polymorphisms which none of the studies considered these issues.

5. Conclusions

Based on what was discussed, we found that serum vit D significantly was lower in infertile individuals compared to fertile ones. Moreover, our analysis revealed significant association between vit D and sperm motility and progressive motility. It should be noted that, there was significant heterogeneity among included studies which should be kept in mind when interpreting the results. Further

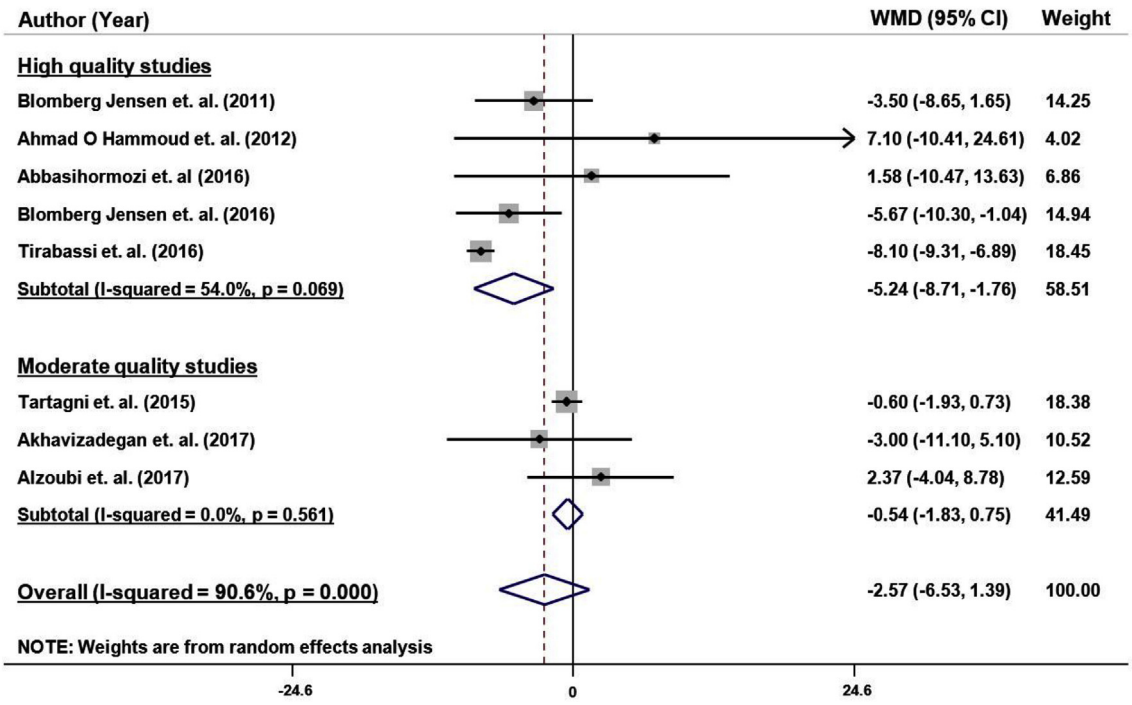

Fig. 8. Forest plot of the association between serum 25(OH)D level and sperm progressive motility.

prospective cohort studies and clinical trials are needed for better understanding of the relationship between vit D and fertility and its components.

Funding

This research received no external funding.

Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

All analyses were based on previous published studies; thus, no ethical approval isrequired.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Author contributions

A. Arab, A. Hadi, G. Askari: contributed in concept of manuscript and edited the draft.

A. Arab, S. Mehrabani, S. P. Mousavian and M. Nasirian, G. Askari contributed in writing and revising the manuscript.

Research registration Unique Identifying number (UIN)

Name of the registry: Prospero database.

Unique Identifying number or registration ID: CRD42019123355.

HyperVlink to the registration (must be publicly accessible): http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019123355.

Guarantor

Arman Arab and Maryam Nasirian are guarantors of this study.

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