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SYSTEMATIC REVIEW

Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background There is currently no systematic review examining the effects of vitamin D supplementation among athletes. A rigorous systematic review and meta-analysis is important to provide a balanced view of current knowledge on the effect of vitamin D on serum 25-hydroxyvitamin D [25(OH)D] concentrations and physical performance.

Objectives This systematic review of randomized controlled trials (RCTs) evaluated the effects of oral vitamin D supplementation on serum 25(OH)D concentrations and physical performance in athletes.

Methods Multiple electronic databases were searched, and study eligibility, methodological quality assessment, and data extraction were completed independently and in duplicate. Studies were stratified by baseline vitamin D sufficiency, season, and latitude. A cut-off of 30 ng/ml (75 nmol/l) of 25(OH)D was used for sufficiency. Absolute mean differences (AMDs) between vitamin D and placebo using random effects analysis, and heterogeneity using Q statistic and I^2 index, were calculated. AMD with 95% confidence interval (CI), p value, and I^2 are reported.

Results In total, 13 RCTs (2005–2016) with 532 athletes (vitamin D 311, placebo 221) were eligible. A total of 433 athletes (vitamin D 244, placebo 189) had complete outcome data. Among athletes with baseline values suggesting insufficiency, vitamin D supplementation led to significant increases from 3000 IU (AMD 15.2 ng/ml; 95% CI 10.7–19.7, $p < 0.0001$, $I^2 = 0\%$) and 5000 IU (AMD 27.8 ng/ml; 95% CI 16.9–38.8, $p < 0.0001$, $I^2 = 78\%$) per day at >45° latitudes. Both doses led to sufficiency concentrations during winter months. Among athletes with baseline vitamin D suggesting sufficiency, serum 25(OH)D sufficiency was maintained from different doses at both latitudes. Of 13 included trials, only seven measured different physical performances and none demonstrated a significant effect of vitamin D supplementation during 12 weeks of follow-up.

Conclusion Despite achieving sufficiency in vitamin D concentrations from ≥3000 IU supplementation, physical performance did not significantly improve. Between-study heterogeneity was large, and well-designed RCTs examining the effect of vitamin D supplementation on serum 25(OH)D concentrations, physical performance, and injuries in different sports, latitudes, ethnicities, and vitamin D status are needed.

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Key Points

Vitamin D supplementation of >3000 IU/day led to significant increases in vitamin D concentrations and achieved sufficiency among athletes with insufficient vitamin D concentrations in latitudes where there is little sun exposure in winter months.

The continuous consumption of <2000 IU may lead to sufficiency in vitamin D concentrations during spring/summer and maintain sufficiency throughout the wintertime.

Despite achieving sufficiency in vitamin D concentrations, physical performance across seven trials did not significantly improve.

1 Introduction

Vitamin D supplementation is becoming a prevailing area of sports medicine because of its role in musculoskeletal health, physical performance, and stress fractures [1, 2]. Higher concentrations of vitamin D intake are recommended to assure adequate availability in metabolic pathways for optimal performance [3]. There are two main forms of vitamin D, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), which are obtained from different sources such as diet, ultraviolet B radiation exposure, and supplements. Both forms are transformed to serum 25-hydroxyvitamin [25(OH)D] in the liver and can be measured in blood samples [4]. In the kidney, 25(OH)D is further transformed into the biologically active compound calcitriol ($1,25(OH)_2D$) [5, 6]. 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) stimulates intestinal absorption of calcium and phosphate for new bone formation [5]. Most cells and tissues possess vitamin D receptors (VDRs) to convert vitamin D to its active form [6, 7], and calcitriol binds to VDRs in the cell nucleus before exerting a broad range of actions within the body [7–9]. The effects of vitamin D on musculoskeletal health are well established in the literature, and the dietary recommendations for vitamin D have been revised recently based on these findings worldwide [10, 11]. VDRs regulate gene expression for essential body functions and have been found within all body tissues [3]. Thus, the presence of VDRs in body tissues suggests a significant role of vitamin D in musculoskeletal health [2–4]. Ogan and Pritchett [3] proposed two possible mechanisms by which the presence of VDRs in body tissues suggest a role in musculoskeletal health. The first mechanism includes a direct role of $1,25(OH)_2D$ in VDRs within muscle cells. The second explanation might be that "vitamin D modifies the transportation of calcium in sarcoplasmic reticulum by increasing the efficiency of calcium bindings involved in muscle contraction" [3]. It is also suggested that the beneficial effects of vitamin D supplementation on muscle strength could be due to an increase in the size and amount of type II (fast twitch) muscle fibers [3, 4]. These findings in regard to musculoskeletal health and vitamin D status may affect physical performance and prevent injury in athletes [3]. Recently published articles have described the effect of exercise/training type on increasing 25(OH)D via increased lipolysis. Chang and Kim [12] studied the effects of the most hormonally active form of vitamin D 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] on adipocyte fat storage and lipid metabolism in mature 3T3-L1 cells and found that "vitamin D might improve adipocyte metabolic function and protect against obesity". Another study [13] found that vitamin D supplementation of 83 μg (3320 IU) might improve several cardiovascular disease risk markers in overweight subjects.

There is debate among experts regarding healthy serum 25(OH)D concentrations and the minimum required daily vitamin D intake. The Endocrine Society Committee (ESC) has defined concentrations of ≥30 ng/ml (≥75 nmol/l) as sufficient, 21–29 ng/ml (52.5–72.5 nmol/l) as insufficient, and ≤20 ng/ml (≤50 nmol/l) as deficient [10, 14]. The 2016 global recommendations suggested >20 ng/ml (>50 nmol/l) concentrations as sufficient, 12–20 ng/ml (30–50 nmol/l) as insufficient, and <12 ng/ml (<30 nmol/l) as deficient [11]. A concentration of >30 ng/ml is recommended for stable parathyroid hormone concentrations and maximal gastrointestinal absorption of calcium [3], whereas concentrations of 100 ng/ml (250 nmol/l) may contribute to vitamin D toxicity [11]. Because of the intense physical activities of athletes, a cut-off of ≥30 ng/ml (≥75 nmol/l) is suggested for vitamin D sufficiency [15] and >20 ng/ml (>50 nmol/l) for insufficiency [3]. Holick [16] suggested that it would take years of very high doses of vitamin D to cause vitamin D toxicity and hypercalcemia. In terms of the daily vitamin D intake required to maintain healthy serum 25(OH)D concentrations in adolescents aged ≤18 years and adults aged 19–70 years, the ESC [10] recommends 600–1000 IU with an upper limit of 4000 IU and 1500–2000 IU with an upper limit of 10,000 IU, respectively. The Institute of Medicine (IOM) suggests 600 IU with an upper limit of 4000 IU for individuals aged 9–70 years [17]. However, recommendations vary from 600 to 7000 IU depending on factors such as age, geographic location, skin pigmentation, physical activities, and season [18].

Low concentrations of vitamin D have been reported in young and active populations, including athletes

[7–9, 14, 15, 19], with respect to the recommended concentration of >30 ng/ml considered sufficient by the ESC [10] and have been shown to negatively impact musculoskeletal and immune function [3, 20]. Recent publications suggest higher rates of vitamin D insufficiency (<30 ng/ml) in athletes, particularly at higher latitudes, in late fall and wintertime, and with indoor activities; in addition, there is an indication that lower extremity stress fractures are related to vitamin D insufficiency in military personnel [15, 21]. Sports medicine physicians are primarily concerned with athletes' performance, and in turn vitamin D insufficiency among athletes has received growing interest.

2 Rationale and Objectives

Current overviews have discussed the effect of vitamin D on muscle function and physical performance [22, 23]; however, there is no systematic review examining the effects of vitamin D supplementation among athletes. The published literature consists of small trials with null effect findings, but this could be due primarily to low statistical power rather than to a true lack of biological effect. A rigorous systematic review and meta-analysis is hence important to provide a balanced view of current knowledge based on improved statistical power. This systematic review and meta-analysis was designed to examine the effects of oral vitamin D supplementation primarily on total serum 25(OH)D concentrations and, second, on the physical performance of athletes. We hypothesized that there is a dose–response effect of vitamin D on 25(OH)D.

3 Methods

3.1 Design

This systematic review and meta-analysis was conducted using a predefined protocol. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [24] was used to ensure rigorous methodology and reporting. The PRISMA statement consists of a flow diagram and a checklist.

3.2 Eligibility Criteria

The PICO approach was used to frame the research question as follows:

- Population (P) was defined as male and female athletes aged 10–40 years involved in any sport activities. The age range was decided based on our previous publication on the prevalence of vitamin insufficiency in athletes [15]. In the 23 included studies, the age of athletes varied from 11–39 years.
- Intervention (I) was oral vitamin D supplementation, not limited to any dosage or duration.
- Comparison (C) was placebo or no intervention.
- Outcomes (O) were primarily 25(OH)D and, second, physical activities and sport-related injuries.

Only randomized controlled trials (RCTs) were included. The eligibility criteria were set to target all trials conducted in athletes and were not limited to endurance training or optimal aerobic and anaerobic performance. Non-randomized trials, abstracts, non-athlete-related trials, and multivitamin supplementation were excluded. Athletes with chronic illness that could influence 25(OH)D concentrations or alter responses to vitamin D were excluded. Trials assessing solar radiation were not included to avoid further heterogeneity due to different methods of intervention assessment. Abstracts were excluded on the basis of insufficient information on quality and outcome assessment and findings derived from incomplete data.

3.3 Search Methods for Identification of Articles

An electronic literature search of the MEDLINE, PubMed, CINAHL, Embase, SPORTDiscus, and Cochrane Library databases from inception to May 2016 was completed with the guidance of a professional medical librarian. Combinations of the following search terms and medical subject headings (MeSH) were used: vitamin D, 25-hydroxyvitamin D, 25(OH)D, cholecalciferol, calcidiol, 25-hydroxycholecalciferol, exercise, athletes, sports, athletic performance, physical fitness (Electronic Supplementary Material [ESM], Appendix S1). The search results were merged and duplicates were removed. The search was updated using PubMed in October 2016 to retrieve the most recent publications.

3.4 Eligibility Assessment, Study Selection, and Quality Assessment

Covidence (http://community.cochrane.org/tools/review-production-tools/covidence) is an online Cochrane primary screening and data extraction tool that has inbuilt key steps including the PRISMA flow diagram and the Cochrane risk of bias assessment tool (http://www.cochrane.org). This platform was used to screen, select, and assess the quality of the included trials. The quality assessment tool is designed to evaluate RCTs for sources of bias in the following domains: selection, performance, detection, attrition, reporting, and other sources. The trial was scored as low risk if adequately described, high risk if

not described, and unclear if inadequately described. We were unable to assess reporting bias because of the lack of access to protocols.

The citations from the initial search after excluding duplicates were uploaded in Covidence. The review articles were cross-referenced to identify additional articles. Titles and abstracts were reviewed for eligibility in duplicate and independently. Two authors then independently reviewed the full texts of the selected articles for further eligibility. The reviewers then independently assessed the methodological quality. Disagreements were resolved through consensus.

3.5 Data Extraction

Data were recorded on a data extraction form designed and piloted a priori using Microsoft® Excel software. Data were collected independently and in duplicate. Disagreements were resolved through consensus. The geographical location, latitudes, and the start and end date of the trial were collected. Latitudes were retrieved from the website http://www.worldatlas.com if not reported. Data pertaining to athletes' demographics (mean age, standard deviation [SD], sex, sport activity), vitamin D (unit, dosages, product, and duration), and outcome measures (mean, SD, unit) at baseline and at follow-ups were extracted.

Vitamin D intake is measured in international units (IU) or micrograms (μg), where 100 IU is equal to 2.5 μg [25]. For consistency, we converted (http://www.nafwa.org/vitamind.php) units originally reported in μg to IU. The timing and dosage of supplementation varied between trials. We converted them into daily dosages whenever reported in weekly intervals. The ESC recommendation of 1500–2000 IU cut-off for adults aged 19–70 years with an upper limit of 10,000 IU [17] was used for dosage grouping. Serum 25(OH)D is measured in nanogram per milliliter (ng/ml) or nanomoles per liter (nmol/l), where 1 ng/ml is equal to 2.496 nmol/l [3]. We converted and reported measurements in both units for consistency but used ng/ml for data analysis (http://www.endmemo.com/medical/unitconvert/Vitamin__D.php). SD was extracted from range, standard errors, confidence intervals (CIs) or p values if not reported. Means were retrieved from authors if medians were reported. The cut-off of >30 ng/ml (>75 nmol/l) for vitamin D sufficiency recommended by the ESC for a young healthy population was used for the analysis [10, 14]. This serum concentration is required for stable parathyroid hormone concentrations and reduced risk of secondary hypoparathyroidism [3].

3.6 Data Stratification and Subgroups

During data extraction, we noted that many trials targeted athletes with insufficient vitamin D (<30 ng/ml [75 nmol/l]) status during fall and winter when sun exposure is minimal. Trials were also divided into 31°–37° and 47°–53° latitudes. The follow-up was approximated at 1, 6, 12, and 24 weeks. For homogeneity and consistency, trials were stratified by baseline vitamin D sufficiency (≥30 ng/ml), season (fall/winter and spring/summer), and latitude (<40° and >45°) and were analyzed for each stratum separately. The pooled 25(OH)D was weighted by duration of intervention and reported at the follow-up for each subgroup.

3.7 Data Synthesis

For within-group effects, we calculated the weighted mean 25(OH)D at pre- and post-supplementation for vitamin D and placebo. For between-group effects, we estimated the absolute mean differences (AMDs) in mean 25(OH)D (after adjusting for baseline values) between vitamin D and placebo at each follow-up using a random-effects model and an inverse variance approach. Heterogeneity was tested using the Cochran's Q test with p value set at 0.1 for significance and quantified using the I^2 statistic (I^2 <40% as low, 40–60% as moderate, and >60% as substantial heterogeneity). A funnel plot was used for visual assessment of publication bias. Pooled AMDs with 95% CIs are reported. A p value of 0.05 was used for statistical significance. SPSS 22.0 (http://www.ibm.com/) and Review Manager 5.3 (http://www.cochrane.org) were used for analyses. The sensitivity analysis was performed excluding trials with $>\approx 15\%$ missing outcome data. The PRISMA checklist was completed to adhere to the Cochrane reviews guidelines. The 27 checklist items pertain to title, abstract, methods, results, discussion, and funding of the meta-analysis.

4 Results

4.1 Eligibility Assessment and Article Selection

Figure 1 summarizes the search and selection process. After reviewing 1102 titles and abstracts, 32 articles were selected for full-text article review. Of the 32 articles, 12 RCTs were included in this meta-analysis [26–38]. One was added during the search update [26] (Fig. 1). The level of agreement was 76.5% (66–87%) for the title and abstract screening and 80% (59–100%) for full-text review eligibility.

4.2 Publication Bias

Figure 2 presents the funnel plot of the included trials for 25(OH)D. The horizontal axis presents effect size, and the vertical axis presents standard error. The funnel seems somewhat symmetric, indicating low publication bias.

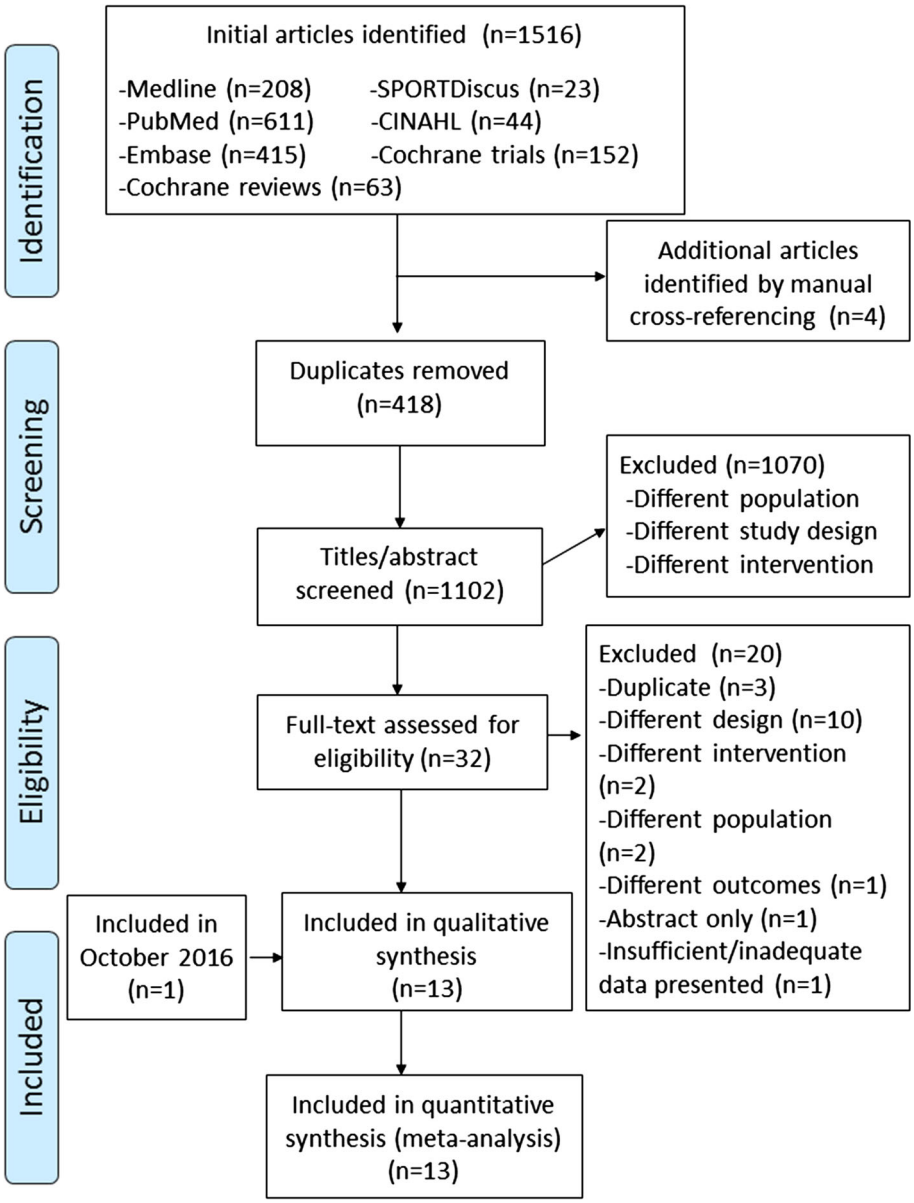

Fig. 1 PRISMA flow diagram of search and selection process

4.3 Risk of Bias Assessment

The methodological quality of the trials and introduced risk of bias are shown in Fig. 3. Six trials did not report the randomization sequence generation method and allocation concealment. However, with the exception of two trials, all were placebo controlled and double blinded. Guillemant et al. [30] paired the athletes for height, weight, and Tanner pubertal stage and randomly assigned them to vitamin D_3 or control groups. Backx et al. [26] classified the vitamin D status of athletes as either sufficient or insufficient and randomized athletes with insufficient vitamin D into three different doses and used those with sufficient vitamin D as controls. The remaining trials, except for Storlie et al. [36], were clearly stated as being double-blind studies and had placebos that were virtually identical to vitamin D. Investigators in the Storlie et al. [36] trial randomized athletes to 1000 IU vitamin D or placebo oral spray manufactured by different companies; as such, it was unclear whether blinding was achieved. Four trials had lost more than 20% of the outcome data. Only four presented a flow diagram [26, 29, 35, 37]. Other biases included three trials that did not disclose conflicts of interest [27, 30, 34].

4.4 Trials and Participants' Baseline Characteristics

Baseline characteristics are presented in Tables 1 and 2. The latitudes varied from 31°S to 53°N. Five trials were

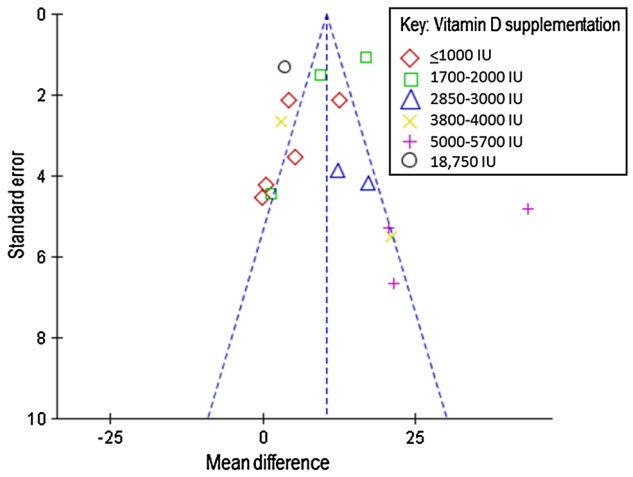

Fig. 2 Funnel plot of the included studies for assessment of publication bias

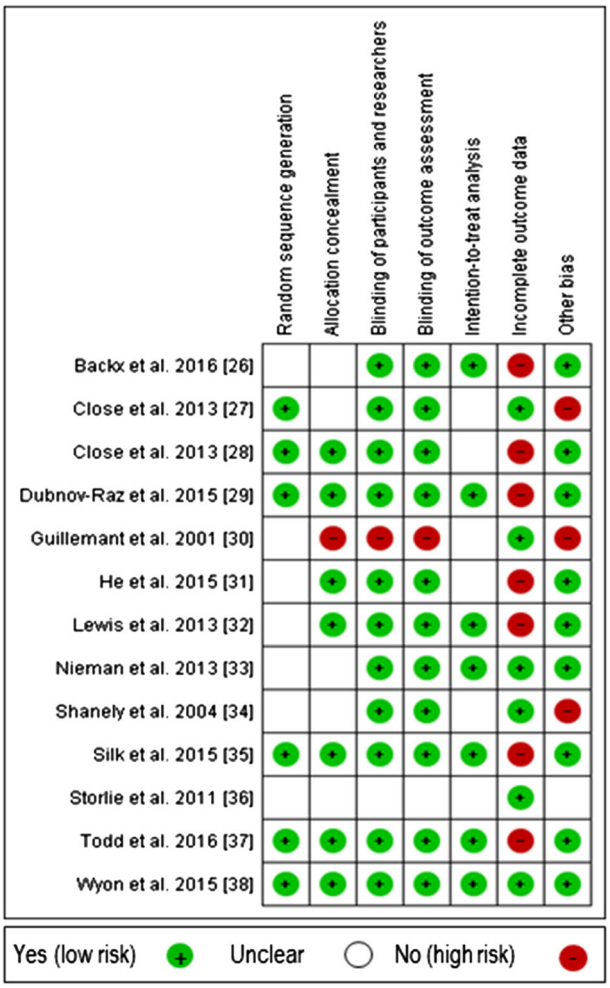

Fig. 3 Cochrane risk of bias assessment

from the UK [27, 28, 31, 37, 38], four from the USA [32–34, 36], and one each from the Netherlands [26], Israel [29], France [30], and Australia [35]. Five trials [26, 32, 35–37] measured dietary vitamin D intake, use of tanning beds, and sun exposure and found no between-group differences. Athletes were engaged in different sports, and 8 of the 13 trials included only males. One trial [33] included NASCAR (National Association for Stock Car Auto Racing) pit crew athletes and did not report sex. The mean age varied from 14 years in swimmers [29, 30] to 29 years in judo athletes [38]. A total of 11 trials supplemented vitamin D_3 (Table 1), and two [33, 34] used vitamin D_2 in the form of soymilk powder and capsules made from portobello mushrooms, respectively [39]. The daily dosage varied from 400 IU for 52 weeks [26] to 18,750 IU for 8 days (bolus of 150,000 IU) [38]. Two trials reported compliance rates of 90% [36] and 70% [32]. The sample sizes varied from 10 to 102 athletes. Trials with longer follow-up reported larger losses of outcome data [26, 32, 35]. The Australian trial [35] allocated 400 IU vitamin D_3 plus 800 mg calcium for 24 weeks from October to May at 31°–37°S latitudes. Many athletes were relocated or were racing on the day of outcome data collection. Backx et al. [26] randomly allocated 400, 1100, or 2200 IU to athletes with insufficient vitamin D and compared them with 13 athletes with sufficient vitamin D from March to March; 32 withdrew and 41 athletes had missing outcome data at various points during the study. A total of 532 athletes were included in 13 trials, with 311 randomized to vitamin D and 221 to placebo (Table 1). A total of 99 athletes had missing outcome data (withdrew or were lost to follow-up), and 433 athletes (vitamin D 244, placebo 189) had complete outcome data (Table 2).

4.5 Stratification and Subgroups

In total, 11 of the trials were conducted in fall and/or winter when sun exposure is minimal. Three trials included athletes with sufficient vitamin D [32, 33, 36]. Silk et al. [35], from Australia, supplemented vitamin D_3 400 IU plus calcium 800 mg in the spring and summer for 24 weeks (October to May at 31°–37°S latitudes). Backx et al. [26] measured 25(OH)D concentrations at 12-week intervals from March 2013 to March 2014. For stratification, the outcome data from March to September were included in the spring/summer strata and data from September to March in the fall/winter strata. A total of 531 athletes were analyzed: 388 with insufficient [26–31, 34, 35, 37, 38] and 143 with sufficient [32, 33, 36] vitamin D status. This is because Backx et al. [26] and Close et al. [28] randomized three and two different doses, respectively, and compared each dosage group with the same control. Therefore, these two trials contributed more outcome data for data synthesis.

Table 1 Characteristics of the included randomized controlled trials

Reference	Country	Latitude	Season	Sports activity	Randomized ($n = 532$)	Vitamin D dosage IU (μg)	Duration	Type	Product
Backx et al. [26]	Netherlands	52°N	All	Mixed sports	29/29/31/13	2200 (55)/day vs. 1100 (27.5)/day vs. 400 (10)/day vs. control	52 weeks	D_3 capsules	DSM Biotechnology Center, DELFT, the Netherlands
Close et al. [27]	UK	53°N	Winter	Soccer	5/5	5000 (125)/day vs. PL	8 weeks	D_3 capsules	Biotech Pharmacal Inc., AZ, USA
Close et al. [28]	UK	53°N	Winter	Mixed sports	10/10/10	20,000 (500)/week vs. 40,000 (1000)/week vs. PL	12 weeks	D_3 capsules	Biotech Pharmacal Inc., AZ, USA
Dubnov-Raz et al. [29]	Israel	31°–32°N	Fall/winter	Swimmers	27/26	2000 (50)/day vs. PL	12 weeks	D_3 drops	CTS Chemical Institutes Ltd., Israel
Guillemant et al. [30]	France	49°N	Fall/winter	Jockeys	29/29	100,000 (2500)/8 weeks vs. control	26 weeks	D_3 solution	Uvésdose, Laboratoires Crinex, Montrouge, France
He et al. [31]	UK	53°N	Fall/winter	Mixed sports	25/25	5000 (125)/day vs. PL	14 weeks	D_3 capsules	Biotech Pharmacal Inc., AZ, USA
Lewis et al. [32]	USA	38°N	Fall/winter	Swimmers/divers	23/22	4000 (100)/day vs. PL	26 weeks	D_3 capsules	Nature Made Pharmavite LLC, Northridge, CA, USA
Nieman et al. [33]	USA	35°N	Fall	NASCAR pit crew	15/15	3800 (95)/day vs. PL	6 weeks	D_2 soymilk powder	Huang and Winters [39]
Shanely et al. [34]	USA	35°N	Winter	Mixed sports	17/17	600 (15)/day vs. PL	6 weeks	D_2 capsules	Huang and Winters [39]
Silk et al. [35]	Australia	31°–37°S	Spring to fall	Jockeys	14/15	400 (10) + 800 mg Ca/day vs. PL	26 weeks	D_3 tablets	USANA Pty Ltd., Sydney, Australia
Storlie et al. [36]	USA	47°N	Fall/winter	Mixed sports	14/13/	1000 (25)/day vs. PL	12 weeks	D_3 spray	Mercola Health Resources, Aurora, IL, USA
Todd et al. [37]	UK	55°N	Fall/winter	Soccer	22/20	3000 (75)/day vs. PL	12 weeks	D_3 spray	BetterYou Ltd, Barnsley, UK
Wyon et al. [38]	UK	52.3°N	Winter	Judo	11/11	150,000 (3750)/one time vs. PL	8 days	D_3 tablets	Not reported

Ca calcium, *PL* placebo

Table 2 Baseline measurements of the included randomized controlled trials

Reference	Analyzed ($n = 433$)	Vitamin D daily dosage	Males (%)	Mean age, years	25(OH)D (ng/ml)	25(OH)D (nmol/l)	25(OH)D method of analysis	Lost to follow-up
Backx et al. [26]	20	2200 IU/day	62	21.0 ± 3.0	20.0 ± 6.0	50.0 ± 15.0	(LC–MS/MS) assay, VU Medical Center, Amsterdam, the Netherlands	41/102 (40%)
	14	1100 IU/day	62	22.0 ± 3.0	19.6 ± 6.4	49.0 ± 16.0		
	16	400 IU/day	58	21.0 ± 3.0	20.0 ± 6.4	50.0 ± 16.0		
	11	Control	0	23.0 ± 4.0	38.1 ± 4.8	95.0 ± 12.0		
Close et al. [27]	5	5000 IU	100	18.0 ± 5.0	11.6 ± 10.0	29.0 ± 25.0	HPLC-MRM (Becton Dickinson, Oxford, UK)	0%
	5	PL			21.2 ± 11.6	53.0 ± 29.0		
Close et al. [28]	6	5714 IU	100	21.0 ± 1.0	20.4 ± 10.4	51.0 ± 26.0	HPLC-MRM (Becton Dickinson, Oxford, UK)	16.7% (5/30)
	10	2857 IU		22.0 ± 2.0	21.2 ± 10.4	53.0 ± 26.0		
	9	PL		21.0 ± 1.0	20.8 ± 10.8	52.0 ± 27.0		
Dubnov-Raz et al. [29]	25	2000 IU	62.3	13.9 ± 1.6	24.4 ± 4.9	60.9 ± 12.2	RIA (DiaSorin Inc., Stillwater, MN, USA)	11.3% (6/53)
	22	PL		14.1 ± 1.8	24.8 ± 4.6	61.9 ± 11.5		
Guillemant et al. [30]	29	1666 IU	100	14.3 ± 0.5	21.5 ± 4.9	53.7 ± 12.2	Competitive Protein Binding Assay (Amersham International, Amersham, UK)	1.7% (1/58)
	28	Control			24.4 ± 6.2	61.0 ± 15.5		
He et al. [31]	20	5000 IU	100	20.1 ± 1.7	22.0 ± 3.7	54.9 ± 4.6	HPLC-MS (Waters Acuity, Manchester, UK)	22% (11/50)
	19	PL		21.0 ± 2.3	22.5 ± 4.3	56.1 ± 5.4		
Lewis et al. [32]	19	4000 IU	59.4	19.0 ± 1.6	52.0 ± 13.7	129.8 ± 34.2	NR (Core of theCenter for Clinical and Translational Science, KY, USA)	28.9% (13/45)
	13	PL		19.0 ± 1.1	64.0 ± 16.7	159.7 ± 41.7		
Nieman et al. [33]	13	3800 IU	NR	27.1 ± 1.5	36.6 ± 6.6	91.4 ± 16.4	HPLC-MS/MS (Shanely et al. [34])	6.7% (2/30)
	15	PL		27.3 ± 0.9	40.7 ± 8.1	101.6 ± 20.2		
Shanely et al. [34]	17	600 IU	100	16.6 ± 0.2	25.1 ± 5.0	62.6 ± 12.5	CLIA (DiaSorin Inc., Stillwater, MN, USA)	2.9% (1/34)
	16	PL		15.9 ± 0.3	26.2 ± 8.0	65.4 ± 20.0		
Silk et al. [35]	8	400 IU + 800 g Ca	100	22.3 ± 5.0	25.9 ± 7.8	64.6 ± 19.5	ELISA (DIALAB)	41.4% (12/29)
	9	PL		19.3 ± 1.8	32.5 ± 9.8	81.2 ± 24.4		
Storlie et al. [36]	14	1000 IU	100	NR	46.9 ± 18.7	117 ± 46.6	Vitamin D assay (LabCorp Seattle, WA, USA)	0%
	13	PL			55.7 ± 18.7	139 ± 46.6		
Todd et al. [37]	17	3000 IU	42.9	20.0 ± 2.0	19.0 ± 5.3	47.4 ± 13.3	HPLC-MS (AB SCIEX, Framingham, MA, USA)	16.7% (7/42)
	18	PL			17.3 ± 8.8	43.1 ± 22.0		
Wyon et al. [38]	11	18,750 IU	100	29.0 ± 10.6	13.2 ± 3.8	32.8 ± 9.4	ECLIA (Tecan Infinite F500, Mannedorf, Switzerland)	0%
	11	PL		26.0 ± 7.4	16.3 ± 2.7	40.7 ± 6.8		

Data are mean ± standard deviation unless stated otherwise

25(OH)D 25-hydroxy vitamin D, *Ca* calcium, *CLIA* chemiluminescent immunoassay, *ECLIA* electrochemiluminescent immunoassay, *ELISA* enzyme-linked immunosorbent assay, *HPLC MRM* high-performance liquid chromatography tandem multiple reaction mode, *HPLC-MS* high-performance liquid chromatography-tandem mass spectrometry, *LC–MS/MS* liquid chromatography mass spectrometry, *NR* not reported, *PL* placebo, *RIA* radioimmunoassay

4.6 Serum 25(OH)D Concentrations

4.6.1 Within-Group Effects

Table 3 presents the mean 25(OH)D concentration at pre- and post-supplementation for both vitamin D and placebo arms for individual trials. Table 4 presents the weighted mean 25(OH)D at pre- and post-supplementation and the mean change from pre-supplementation for both vitamin D and placebo arms for different categories.

4.6.1.1 Vitamin D Arm For athletes with insufficient vitamin D status, the mean 25(OH)D increased from pre-supplementation for all seasons and latitudes (Table 4). In

Table 3 Baseline and follow-up serum 25(OH)D concentrations

Reference	Latitude	Time	Vitamin D daily dosage	Baseline	$N = 433$	Serum 25(OH)D concentrations[a]					
						1 week	6 weeks	12 weeks	24 weeks	36 weeks	48 weeks
Backx et al. [26]	52°N	Mar–Mar	2200 IU	20.0 ± 6.0	20			37.6 ± 7.6	57.7 ± 13.2	48.1 ± 11.2	40.0 ± 10.8
			1100 IU	19.6 ± 6.4	14			31.6 ± 7.2	47.6 ± 10.8	34.0 ± 10.0	30.4 ± 11.6
			400 IU	20.0 ± 6.4	16			32.0 ± 6.8	44.4 ± 12.4	34.0 ± 8.4	32.4 ± 10.4
			None	38.0 ± 4.8	11			40.0 ± 8.8	51.7 ± 12.8	40.8 ± 9.6	38.4 ± 8.8
Close et al. [27]	53°N	Nov–Jan	5000 IU	11.6 ± 10.0	5		41.3 ± 10.0				
			Placebo	21.2 ± 11.6	5		29.6 ± 9.6				
Close et al. [28]	53°N	Jan–Apr	5714 IU	20.4 ± 10.4	6		39.3 ± 5.6	36.5 ± 9.6			
			2857 IU	21.2 ± 10.4	10		31.7 ± 5.6	34.1 ± 4.0			
			Placebo	20.8 ± 10.8	9		14.8 ± 7.2	16.4 ± 8.8			
Dubnov-Raz et al. [29]	31°–32°N	Nov–Jan	2000 IU	24.4 ± 4.9	25			29.2 ± 6.5			
			Placebo	24.8 ± 4.6	22			20.3 ± 4.2			
Guillemant et al. [30]	49°N	Sep–Mar	1666 IU	21.5 ± 4.9	29				22.1 ± 4.6		
			Control	24.4 ± 6.2	28				8.1 ± 0.2		
Guillemant et al. [30]	53°N	Nov–Feb	5000 IU	22.0 ± 3.7	20			58 ± 7.0			
			Placebo	22.5 ± 4.3	19			15 ± 1.6			
Lewis et al. [32]	38°N	Sep–Mar	4000 IU	52.0 ± 13.7	19			60 ± 19.9	53 ± 16.9		
			Placebo	64.0 ± 16.7	13			52 ± 18.4	44 ± 14.4		
He et al. [31]	35°N	Dec–Jan	3800 IU	36.6 ± 6.6	13		37.4 ± 6.9				
			Placebo	40.7 ± 8.1	15		38.6 ± 7.0				
Shanely et al. [34]	35°N	Jan–Feb	600 IU	25.1 ± 5.0	17		27.8 ± 5				
			Placebo	26.2 ± 8.0	16		24.8 ± 7				
Lewis et al. [32]	31°–37°S	Oct–May	400 IU	25.9 ± 7.8	8				32.8 ± 4.3		
			Placebo	32.5 ± 9.8	9				26.9 ± 4.3		
Storlie et al. [36]	47°N	Oct–Jan	1000 IU	46.9 ± 18.7	14			37.9 ± 7.4			
			Placebo	55.7 ± 18.7	13			41.2 ± 20.6			
Nieman et al. [33]	55°N	Nov–Apr	3000 IU	19.0 ± 5.3	17			33.5 ± 13.2			
			Placebo	17.3 ± 8.8	18			19.7 ± 10.2			
Wyon et al. [38]	52.3°N	Feb	18,750 IU	13.2 ± 3.8	11	16.8 ± 3.2					
			Placebo	16.3 ± 2.7	11	16.3 ± 2.6					

Data are mean ± standard deviation unless stated otherwise

[a] Measurements are in ng/ml

Table 4 Pre- and post-supplementation pooled mean 25(OH)D concentrations in vitamin D and placebo arms for different categories

Baseline	Vitamin D daily dosage IU (μg)	Weeks	Vitamin D supplementation[a]				Placebo[a]			
			$N = 291$	Pre	Post	Change	$N = 240$[b]	Pre	Post	Change
Insufficient vitamin D ($N = 388$)										
Fall/winter ($N = 277$)										
<40°N	≤2000 (<50)	12	42	24.68 ± 4.9	28.78 ± 5.9	4.10	38	25.33 ± 6.0	22.28 ± 5.4	−3.01
>45°N	1666 (41.65)	24	29	21.50 ± 4.9	22.10 ± 4.6	0.60	28	24.4 ± 6.2	8.10 ± 0.2	−16.3
	2850–3000 (71–75)	12	27	20.19 ± 7.2	33.30 ± 8.6	13.11	27	19.60 ± 9.4	17.58 ± 9.1	−2.02
	5000–5714 (125–129)	12	31	20.08 ± 6.0	43.33 ± 9.0	23.25	33	21.62 ± 7.2	17.00 ± 6.7	−4.62
	18,750 (3750)	1	11	13.16 ± 3.7	16.76 ± 3.2	3.60	11	16.30 ± 2.7	16.29 ± 2.6	−0.004
Spring/summer ($N = 111$)										
>45°N	≤2200[c]	24	69	20.59 ± 6.4	41.55 ± 9.4	20.95	42	36.98 ± 5.8	44.10 ± 10.0	7.02
Sufficient vitamin D ($N = 143$)										
Fall/winter										
<40°N	3800–4000 (95–100)	24	32	48.07 ± 6.79	51.02 ± 15.3	2.95	28	55.48 ± 7.7	44.56 ± 12.9	−10.91
>45°N	≤2200[c] (≤55)	24	50	50.09 ± 13.7	37.34 ± 10.0	−12.75	33	52.76 ± 14.4	39.91 ± 11.1	−12.85

Data are presented as mean ± standard deviation unless stated otherwise

[a] Presented in ng/ml

[b] Backx et al. [26] and Close et al. [28] compared multiple doses with one control group. The control group was used for all interventional group comparisons. The findings of Backx et al. [26] were used for both seasons—spring/summer (March–September) and fall/winter (September–March)

[c] Indicates findings are from one study

fall/winter, supplementation of 1666 IU did not result in concentrations of 30 ng/ml being achieved during the 24 weeks [30]. The allocation of ≥3000 IU achieved sufficient concentrations of >30 ng/ml (>75 nmol/l) during 12 weeks of follow-up at >45° latitudes. The 1-week effect from a bolus of 150,000 IU at >45° latitudes was as effective as a 12-week supplementation of 600–2000 IU at <40° latitudes (a small increase of ≈4 ng/ml). During spring and summer time, there was a large increase of 13.92 ng/ml from ≤2200 IU, but the loss of outcome data was 40% for both trials [26, 35]. Athletes with sufficient vitamin D status showed a small increase in the mean 25(OH)D from 3800–4000 IU during the 24 weeks at <40°. For >45° latitudes, there was a large decrease in mean 25(OH)D from ≤2200 IU, but athletes still maintained sufficient vitamin D concentrations at 24 weeks (Table 4).

4.6.1.2 Placebo Arm Mean 25(OH)D was decreased for all categories except in spring/summer time (Table 4). The loss was larger for those who started with sufficient vitamin D concentrations [32, 33, 36] and those who had longer follow-up [30, 32, 35]. Athletes who started with sufficient vitamin D concentrations still maintained sufficiency in fall and winter months.

4.6.2 Between-Group Effects

Figure 4 presents AMDs in 25(OH)D between vitamin D and placebo after adjusting for the baseline values.

Among athletes with baseline values of vitamin D suggesting insufficiency (25(OH)D concentrations of <30 ng/ml), there was a linear trend for dosage and duration. In fall/winter, the AMD in 25(OH)D from 12 weeks of ≤2000 IU was 7.11 ng/ml (95% CI 1.64–12.58, $p = 0.010$, $I^2 = 79\%$), but athletes did not reach sufficiency concentrations of 30 ng/ml (75 nmol/l) at <40° latitudes. For >45° latitudes, AMD from 24 weeks of 1666 IU in an open-label trial [30] was 16.9 ng/ml (95% CI 14.78–19.02), but the difference was more due to loss in the control group than to gain in the vitamin D group

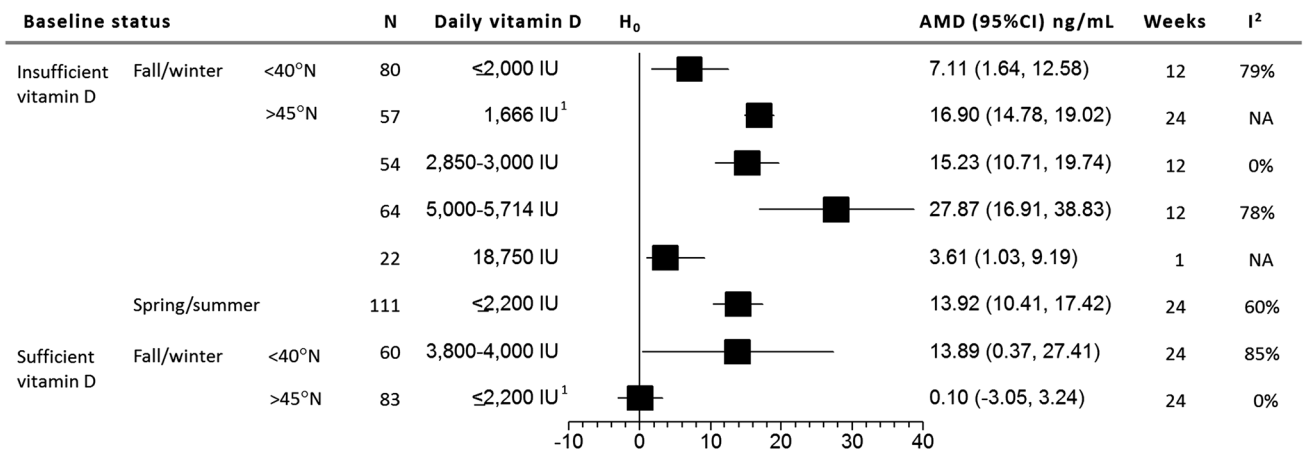

Fig. 4 Forest plot of absolute mean differences in mean serum 25-hydroxyvitamin D (25(OH)D) concentrations between vitamin D supplementation and placebo. *AMD* absolute mean difference (95% CIs) in serum 25(OH)D concentration between vitamin D supplementation and placebo, *CI* confidence interval, H_0 null hypothesis of no difference, I^2 quantification of between-trial heterogeneity, *NA* not applicable. *Boxes with lines* represent the AMD and the boundaries of the confidence intervals. [1]Data obtained from single study

(Table 3). The AMD from a 12-week supplementation of ≅3000 IU (15.23 ng/ml; 95% CI 10.71–19.74, $p < 0.0001$, $I^2 = 0\%$) or ≅5000 IU (27.8 ng/ml, 95% CI 16.91–38.83, $p < 0.0001$, $I^2 = 78\%$) was large, and mean 25(OH)D passed sufficiency concentrations of 30 ng/ml (75 nmol/l) in both groups. The AMD was 13.92 ng/ml (95% CI 10.41–17.42, $p < 0.0001$, $I^2 = 60\%$) for ≤2200 IU in spring/summer [26, 35]. The mean 25(OH)D reached sufficiency concentrations, but there was a 41% loss of outcome data.

For athletes with sufficient vitamin D status, AMD after 24 weeks of 3800–4000 IU was 13.89 ng/ml (95% CI 0.37–27.41, $p = 0.040$, $I^2 = 85\%$) at <40° latitudes in wintertime, but the effect was largely due to the loss in the placebo group than to a gain in the vitamin D group. Nieman et al. [33] supplemented vitamin D 3800 IU in fortified soymilk powder to NASCAR pit crew athletes and reported a gain of only 0.8 ng/ml at 6 weeks. Lewis et al. [32] assigned vitamin D 4000 IU capsules to swimmers and reported a gain of 1 ng/ml at 24 weeks. For >45° latitudes in wintertime [26], gain from ≤2200 IU at 45° latitudes was negligible at 24 weeks (0.10; 95% CI −3.05 to 3.24 ng/ml, $p = 0.950$, $I^2 = 0\%$). The loss in mean 25(OH)D was equally large in both study and placebo arms, but sufficiency was still maintained at March.

4.6.3 Sensitivity Analysis Results

Sensitivity analysis was performed by removing the trials with ≅15% loss of outcome data (Fig. 5). For athletes with insufficient vitamin D status, the data for <40° latitudes did not change (7.11 ng/ml, $I^2 = 79\%$). For >45° latitudes, the AMD of 15.23 ng/ml (95% CI 10.71–19.74, $I^2 = 0\%$) after 12 weeks' supplementation of 3000 IU also remained unchanged. The supplementation of ≥5000 IU still had a large effect of 22.76 ng/ml (95% CI 16.83–28.68, $p < 0.001$, $I^2 = 0\%$) with no heterogeneity. No data were available for spring and summer for athletes with sufficient vitamin D status because of missing outcome data.

4.7 Physical Performance

Seven of 13 trials assessed different physical performances. The sample size in these trials varied from 10 to 47 athletes. The assessment of physical performance varied with sports activities and countries' standards and units of measurement. Table 5 shows the pooled AMD in physical performances between vitamin D and placebo. Hand grip strength (three trials) increased significantly (2.56 kg; 95% CI 1.00–4.13) after 12 weeks' vitamin D supplementation of 2000–3800 IU. No significant differences were found in vertical jump height (0.92 cm; 95% CI −0.55 to 2.44), one repetition maximum (1-RM) bench press (2.05; 95% CI −5.5 to 9.6) or 10- to 30-m sprint (0.04 s; 95% CI −0.04 to 0.12). Table 5 also footnotes the findings from single trials with unit of measurements.

4.8 Injuries

Lewis et al. [32] reported 16 injuries (nine for connective tissue, seven for muscle) for 33 athletes over 24 weeks, and 77% of 16 injuries occurred after an observed decrease in 25(OH)D concentrations (−11 to −47 ng/ml).

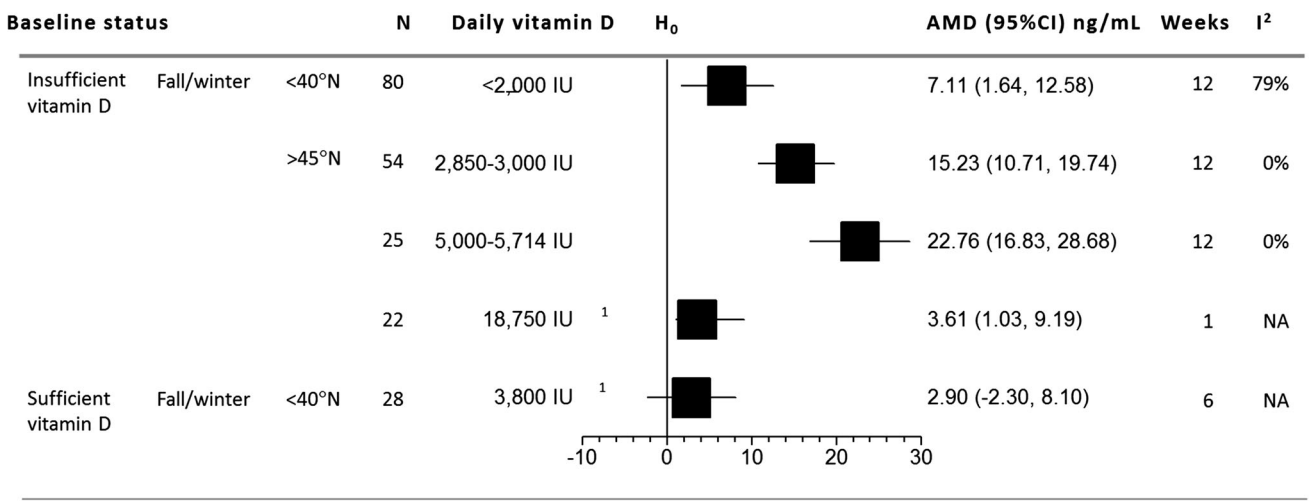

Fig. 5 Forest plot of absolute mean differences in serum 25-hydroxyvitamin D (25(OH)D) concentrations between vitamin D and placebo after removing trials with more than ≈15% loss of outcome data. *AMD* absolute mean difference (95% CIs) in serum 25(OH)D concentration between vitamin D supplementation and placebo, *CI* confidence interval, H_0 null hypothesis of no difference, I^2 quantification of between-trial heterogeneity, *NA* not applicable. *Boxes with lines* represent the AMD and the boundaries of the confidence intervals. [1]Data obtained from single study

Table 5 Pooled mean differences in physical performance between vitamin D and placebo arms

Activities	Number of studies	Sample size	Dose (IU)	Duration (weeks)	AMD (95% CI)
Hand grip strength (kg)	Three [29, 33, 37]	110	2000–3800	12	2.56 (1.0–4.1)
Vertical jump height (cm)	Four [25, 27, 28, 33, 37]	98	2850–5714	12	0.92 (−0.5 to 2.4)
1-RM bench press (kg)	Two [27, 28, 33]	70	2850–5714	12	2.05 (−5.5 to 9.6)
10–30 m sprint (s)	Two [27, 28]	44	2850–5714	12	0.04 (−0.04 to 0.1)

Close et al. [27] did not find significant between-group effects on back squat or Illinois agility test after 6 weeks of 5000 IU. Dubnov-Raz et al. [29, 55] did not find significant between-group differences in swimming performance or upper respiratory infections after 12 weeks of 2000 IU. Nieman et al. [33] did not find significant between-group effects on Wingate, peak power (W/kg), leg-back dynamometer (kg), bench press (3 sets), and Wingate or anaerobic capacity (W/kg) after 6 weeks of 3800 IU. Close et al. [28] did not find significant effects on 1-RM leg press (kg) after 2850 or 5000 IU. Shanely et al. [34] did not find significant between-group effects on vertical jump height (W), leg/back strength (kg/kg) after 6 weeks of 600 IU. Wyon et al. [38] found significant effects on quadriceps (30 °/s) (N m), quadriceps (200 °/s) (N m), hamstrings (30 °/s) (N m) or hamstrings (200 °/s) (N m) after a bolus of 150,000 IU compared with placebo after 1 week

Physical performance measurements from one trial

1-RM 1 repetition maximum, *AMD* absolute mean difference between vitamin D supplementation and placebo, *CI* confidence interval

5 Discussion

5.1 Summary of Main Findings

5.1.1 Serum 25(OH)D Concentrations

A dose-response effect was seen on mean serum 25(OH)D concentrations from vitamin D supplementation. The 12-week supplementation of dosages ≥3000 IU exceeded sufficiency concentrations of 30 ng/ml (75 nmol/l) at higher latitudes in fall and winter time, when there is minimal sun exposure. The findings were consistent with the sensitivity analysis when the trials with ≈>15% missing outcome data were removed and heterogeneity was reduced to 0%. The supplementation of ≤2000 IU in athletes with insufficient vitamin D concentrations did not achieve sufficiency at any latitudes in wintertime [29, 30, 34], whereas 24 weeks of ≤2200 IU [26] achieved sufficiency during spring and summer time, when there is adequate sun exposure [26]. Backx et al. [26] allocated 400, 1100, or 2200 IU to athletes with insufficient vitamin D from March 2013 to March 2014 and compared them with athletes with sufficient vitamin D status. The mean 25(OH)D exceeded 30 ng/ml (75 nmol/l) in June 2013 in

all interventional groups and remained sufficient until March 2014. The current findings are supported by our recent meta-analysis that showed the prevalence of vitamin D insufficiency in athletes also varied by geographical location [15]. These findings suggest that the supplementation of ≥3000 IU in fall and winter will achieve sufficiency during wintertime, when the sun exposure is minimal; whereas the continuous supplementation of ≅2000 IU may achieve and sustain sufficiency in athletes in all geographical locations. This aligns with the ESC's recommendation of 1500–2000 IU for adults. [17]; however, the current findings need to be interpreted with caution because of the limitations and large heterogeneity discussed in detail in Sect. 5.3.

5.1.2 Physical Performance

Seven out of 13 trials assessed a variety of physical performances. The type of performance assessment varied with the sports activities and countries' standards and units of measurement, which made pooling of the data infeasible for activities. In general, two to four trials contributed to the pooling of different physical performances. Three trials that included swimmers, soccer players, or NASCAR pit crew athletes [29, 33, 37] measured hand grip strength, and pooling of the data showed a significant increase after 12-weeks' allocation of ≥2000 IU. The vertical jump height [27, 28, 33, 37], 1-RM bench [27, 28, 33], and 10, 20, or 30 m sprint [27, 28] were not improved significantly. Wyon et al. [38] allocated a bolus dose of 150,000 IU to 11 athletes and found a significant increase in muscle strength at day 8.

5.1.3 Injuries

Lewis et al. [20] reported 16 muscle and connective tissue injuries and related 77% of 16 injuries to decline in 25(OH)D from baseline. None of the trials assessed injuries (stress fractures, muscle, and connective tissue injuries). The UK trials [15, 16, 19] reported nine dropouts or withdrawals from injuries but did not report details on the grouping or timing of the injuries.

5.2 Overview of Published Literature

Our findings are supported by studies on young and healthy groups from the general population. Current systematic reviews and meta-analyses present interesting findings for targeted and specific populations or outcomes. Cashman et al. [40] included 44 RCTs of oral administration of vitamin D_3 <2000 IU/day (50 μg/day) with or without calcium in healthy populations and excluded RCTs of vitamin D_2 and those including higher doses of vitamin D_3. They compared latitudes 40°–49.5°N to >49.5°N and found that intake of 930 IU/day would maintain 25(OH)D >50 nmol/l concentrations. A meta-analysis by Muir and Montero-Odasso [41] included elderly adults aged >60 years and found vitamin D 800–1000 IU to be beneficial for muscle strength and balance. The most recent meta-regression [42] included 88 RCTs of neonates, infants, and adolescents with vitamin D deficiency to assess the effect of a high-dose vitamin D regimen (>1000 IU) on 25(OH)D concentrations. They found rapid normalization of vitamin concentrations (>75 nmol/l) was best achieved by using a loading therapy of >50,000 IU considering disease status, baseline 25(OH)D, and age; however, they found that loading doses of >300,000 IU should be avoided until the risks and benefits are evaluated. Black et al. [43] found a larger effect of vitamin D-fortified food on serum 25(OH)D concentrations in community-dwelling adults with insufficient vitamin D status at latitudes ≥40°N. Similar to our findings, Lewis et al. [44] found significant dose-response effects of vitamin D supplementation on serum 25(OH)D concentrations in youth in the wintertime. They randomly assigned 323 children and adolescents with insufficient vitamin D to 400, 1000, 2000, 4000 IU or placebo and found a significant mean increment in serum 25(OH)D to achieve sufficiency concentrations, except for 400 IU over 12 weeks. It is interesting to note that, whereas 12 weeks of vitamin D 1000 and 2000 IU has significant effects on healthy and active adolescents, the same supplementation did not achieve sufficiency in athletes in the fall and winter at any latitudes. Similar results have been found for military personnel. The USA trial [45] randomized 247 male and female basic military trainees to vitamin D 1000 IU plus calcium 2000 mg or placebo for 6 weeks and found that mean 25(OH)D improved similarly in vitamin D and calcium (pre 23.2, post 28.0 ng/ml) and placebo (pre 20.6, post 24.6 ng/ml) groups. Neither group achieved sufficiency concentrations, but vitamin D and calcium consumption maintained parathyroid hormone concentrations and improved bone density.

Other trials from the USA [46, 47] demonstrated no effects from supplementation with 400 and 1000 IU and only minimal effects from supplementation with 2000 IU on male submariners assigned to a submerged ship. Duplessis et al. [46] supplemented with 400 IU and found serum 25(OH)D significantly decreased in both vitamin D and placebo groups in 49-day submariners. The investigators noticed that a 6-day sunlight exposure compensated for 49-day sunlight absence, but groups did not reach sufficiency concentrations. Gasier et al. [47] randomized 53 submariners with insufficient vitamin D to placebo ($n = 16$), 1000 IU/day ($n = 20$), or 2000 IU/day ($n = 17$) during a 3-month submarine patrol and found mean 25(OH)D increased slightly but that compliance was about

80%. The mean 25(OH)D did not reach sufficiency concentrations in the absence of sunlight exposure; however, 24 weeks of supplementation with 400, 1100, or 2200 IU in athletes [26] achieved and maintained sufficiency when there was adequate sun exposure in late spring and summer. The latter findings are likely influenced by physical activities, vitamin intake from daily diet, and sunlight exposure.

Sufficient vitamin D is important for musculoskeletal health, regulation of electrolyte metabolism, protein synthesis, gene expression, and immune function [1, 2]. Ogan and Pritchett [3] reviewed the risks, recommendations, and benefits of vitamin D supplementation in athletes. They indicated the importance of vitamin D in preventing stress fractures and optimizing bone health, which are of great importance to elite and recreational athletes. Ogan and Pritchett [3] recommended an annual evaluation of vitamin D status for athletes to maintain optimal 25(OH)D concentrations >40 ng/ml. Vitamin D is actively used in numerous physiological pathways. Additional vitamin D intake is recommended to fulfill proper levels of availability, replenishment, and storage in athletes [20, 28, 36]. Similar observations have been reported for navy recruits [48].

Seven trials in the current analysis assessed physical performance and failed to show an association with short-term consumption of vitamin D of any dosage except for hand grip strength. Davids and Baker [54] also commented that currently there is little evidence for the effect of either biological or environmental factors on elite athletic performance. Three meta-analyses assessed the relationship between all forms and doses of vitamin D supplementation and muscle strength (17 RCTs) [49], bone density (23 RCTs) [50], and muscle strength and injuries (ten and four RCTs, respectively) [51] in healthy adults aged ≥18 years and found no strong associations. Ogan and Pritchett [3] also stated that the results of performance trials are not yet convincing enough to support vitamin D as a direct performance enhancer, but resolution of vitamin D insufficiency may have a potential impact on improving performance because of its active role in musculoskeletal health and by possibly maximizing musculoskeletal adaptations to exercise training. They suggested that because of the active role of vitamin D in many metabolic pathways, athletes may require increased intake of vitamin D to assure adequate storage for optimal performance. It is possible that a longer follow-up time is required to show the effect of vitamin D sufficiency on physical performance. This may explain the lack of response in terms of physical performance observed in the UK trials [27, 28], where mean serum 25(OH)D concentrations after 5000 IU supplementation exceeded sufficiency concentrations at 6 and 12 weeks but no change was observed in any physical performance. Wyon et al. [52] provided 2000 IU supplementation to 17 elite classical ballet dancers and compared them with seven controls during winter months. They found significant increases in isometric strength and vertical jump height; however, this small trial was non-randomized and prone to bias [52].

Ogan and Pritchett [3] suggested optimal 25(OH)D concentrations might reduce the risk of debilitating stress fractures among athletes, which may indirectly influence physical performance through prevention of injury. Other overviews have also reported the role of vitamin D deficiency in muscle weakness [19], which may contribute to increased risk of falls and fractures. None of the trials in the current review measured the impact of vitamin D on injuries in terms of 25(OH)D concentrations. Lappe et al. [48] randomized 5201 female navy recruits to vitamin D 800 IU and calcium 2000 mg or placebo and found a significantly reduced incidence of stress fractures in the vitamin D and calcium group; nonetheless, they did not assess its association with improved 25(OH)D concentration. Another longitudinal prospective study of 1082 UK initial military trainees found a significantly higher incidence of stress fractures in those with 25(OH)D concentrations <50 nmol/l (20 ng/ml) at 1 year [53]. One controlled study from the UK [52] found fewer injuries in elite ballet dancers receiving supplementation with vitamin D 2000 IU compared with controls at 52.3°N latitude in the wintertime.

5.3 Strengths and Limitations

The current study has certain limitations inherent to systematic reviews and the included trials. The sample sizes in most trials were small, varying from 10 to 57. There was large between-study heterogeneity related to the PICO components. The populations studied were diverse, reflecting the different sporting activities and sex of the athletes. Sports activities in the included trials varied from mixed sports to a variety of single sports. Some trials included all male athletes [27, 28, 30, 31, 34–36, 38]. The nature, dosage, frequency, duration, and timing of the intervention varied between trials. The majority of supplements were vitamin D_3 tablets or capsules; however, one trial used vitamin D_3 drops [29], one used soymilk powder in plastic containers [33], one in the form of a solution [30], and two oral sprays [36, 37]. Two trials supplemented vitamin D_2 in soymilk powder and in the form of tablets [33, 34]. The majority of trials supplemented vitamin D daily, but some used different frequencies of supplementation. Close et al. [28] supplemented weekly capsules, Guillemant et al. [30] provided a 100,000 IU solution every 8 weeks and Wyon et al. [38] allocated a one-time bolus of 150,000 IU. Two trials

[26, 30] were not placebo controlled. Guillemant et al. [30] paired athletes for height, weight, and Tanner pubertal stage and randomly assigned them to vitamin D or control. Backx et al. [26] randomized athletes with insufficient vitamin D to three different doses and compared them with athletes who had sufficient vitamin D status at baseline; they recorded a 40% loss to follow-up, mostly in the interventional groups. More than half of the trials did not report the method of allocation concealment or random sequence generation. Incomplete outcome data varied from 0 to 40%. These factors most likely were the cause of between-study heterogeneity in some strata. Due to variations in the type and measurement of athletic performance and the diverse standards and units of measurements between countries, pooling of physical performance measures was less feasible. Davids and Baker [54] explained the interactive influence of genetic and environmental constraints such as psychological and physical development, length and expense of involvement in training on elite athletic performance and that the prediction of athletic performance is limited with uncertainty.

This current systematic review and meta-analysis also has certain strengths. The PRISMA criteria of Cochrane reviews were used to ensure sound and rigorous methodology. The PRISMA checklist is attached as Appendix S2 in the ESM. The selection and review process was independently conducted by two or more reviewers. For homogeneity and consistency, the effects of athletes' vitamin D status, location, and season were minimized by stratification. Despite between-trial differences, the direction of effect was consistently in favor of supplementation. The findings are generalizable to all athlete populations. The sensitivity analysis was performed to remove the bias introduced from missing outcome data. The findings of the sensitivity analysis were concordant with the main findings, thereby maintaining generalizability. The heterogeneity of the studies was to be expected, given that sports and participants in them differ substantially. Different sports have different effects on body systems, different physical and mental demands, and different rates of impaired vitamin D status. Hence, it is to be expected that studies would differ significantly in their methodologies, populations examined, supplementation protocols, and performance tests used. For example, if a trial conducted in tennis players (outdoors) showed a significant improvement but one involving karate fighters (indoors) did not, a meta-analysis or large pooled trial that showed an overall net null effect would be misleading with respect to the tennis players. On the other hand, improvement in handgrip strength can be more important in some sports such as judo or tennis and less so in runners or swimmers. For these reasons, the current meta-analysis was planned to minimize heterogeneity by stratification and examined the effect of vitamin D supplementation, adjusting for latitudes, season baseline vitamin D status, vitamin D dosage, and duration; however, it was not feasible to adjust for different sport types. The finding of no effect in the included trials could have been due primarily to low statistical power or to a lack of true biological effect. More high-quality RCTs in different athletic populations, designed to address the limitations of prior studies in the field, are needed. The level of current evidence was estimated as low to moderate for serum 25(OH)D concentrations and very low for physical performance.

5.4 Implications for Research and Practice

To establish successful strategies for sports medicine for optimizing vitamin dosage and serum 25(OH)D concentrations, promoting physical performance and preventing injuries in athletes, researchers are recommended to consider targeting the following:

1. Establishing an optimal dosage (baseline vitamin D status), frequency (daily, weekly, monthly), and duration (short-term for achieving sufficiency or continuous for maintaining sufficiency) for vitamin D supplementation.
2. Assessing 25(OH)D concentrations, physical performance, and injuries concurrently to aptly relate the effects of supplementation on 25(OH)D and consequent physical performance and injuries.
3. Establishing the optimal frequency (every 4 or 6 weeks) of serum 25(OH)D assessment.
4. Establishing the optimal time for physical performance assessments as it might take a longer time to observe the effect, especially on endurance training. This is also important to unify the units of measurement for future studies and meta-analyses.

6 Conclusion

The current evidence found that the supplementation of ≥3000 IU/day led to significant increases in vitamin D concentrations and achieved sufficiency among athletes with insufficient vitamin D concentrations in latitudes where there is little sun exposure in winter months; furthermore, continuous consumption of 2000 IU might lead to sufficiency concentrations during spring/summer and may be maintained throughout wintertime. Despite achieving sufficiency in vitamin D concentrations, physical performance across all studies did not significantly improve. Given the large heterogeneity due to differences in the study populations, interventions, outcomes, design, and methodology of the included trials, well-designed

RCTs are needed to assess the impact of vitamin D supplementation on different athletes. The effect of vitamin D supplementation on serum 25(OH)D concentrations, physical performance, and injuries should be examined in different sports, at varying latitudes, in diverse ethnicities, and in athletes with different baseline vitamin D status.

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Compliance with Ethical Standards

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References

1. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84(1):18–28.
2. Tomlinson PB, Joseph C, Angioi M. Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis. J Sci Med Sport. 2015;18(5):575–80.
3. Ogan D, Pritchett K. Vitamin D and the athlete: risks, recommendations, and benefits. Nutrients. 2013;5(6):1856–68.
4. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86(1):50–60.
5. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 2004;80(6 Suppl):1689S–96S.
6. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81.
7. Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. 2010;95(2):471–8.
8. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122(2):398–417.
9. Prietl B, Treiber G, Pieber TR, et al. Vitamin D and immune function. Nutrients. 2013;5(7):2502–21.
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
11. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab. 2016;101(2):394–415.
12. Chang E, Kim Y. Vitamin D decreases adipocyte lipid storage and increases NAD-SIRT1 pathway in 3T3-L1 adipocytes. Nutrition. 2016;32(6):702–8.
13. Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr. 2009;89(5):1321–7.
14. Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. Public Health Nutr. 2011;14(5):938–9.
15. Farrokhyar F, Tabasinejad R, Dao D, et al. Prevalence of vitamin D inadequacy in athletes: a systematic-review and meta-analysis. Sports Med. 2015;45(3):365–78.
16. Holick MF. Vtamin D is not as toxic as was once thought: a historical and an up-to-date perspective. Mayo Clin Proc. 2015;90(5):561–4.
17. Golden NH, Carey DE. Vitamin D in health and disease in adolescents: when to screen, whom to treat, and how to treat. Adolesc Med State Art Rev. 2016;27(1):125–39.
18. Viljakainen HT, Natri AM, Karkkainen M, et al. A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention. J Bone Miner Res. 2006;21(6):836–44.
19. Holick MF. The vitamin D epidemic and its health consequences. J Nutr. 2005;135(11):2739S–48S.
20. Willis KS, Peterson NJ, Larson-Meyer DE. Should we be concerned about the vitamin D status of athletes? Int J Sport Nutr Exerc Metab. 2008;18(2):204–24.
21. Dao D, Sodhi S, Tabasinejad R, et al. Serum 25-hydroxyvitamin D levels and stress fractures in military personnel: a systematic review and meta-analysis. Am J Sports Med. 2014;43(8):2064–72.
22. Tenforde AS, Sayres LC, Sainani KL, et al. Evaluating the relationship of calcium and vitamin D in the prevention of stress fracture injuries in the young athlete: a review of the literature. PMR. 2010;2(10):945–9.
23. von Hurst PR, Beck KL. Vitamin D and skeletal muscle function in athletes. Curr Opin Clin Nutr Metab Care. 2014;17(6):539–45.
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
25. Angeline ME, Gee AO, Shindle M, et al. The effects of vitamin D deficiency in athletes. Am J Sports Med. 2013;41(2):461–4.
26. Backx EM, Tieland M, Maase K, et al. The impact of 1-year vitamin D supplementation on vitamin D status in athletes: a dose-response study. Eur J Clin Nutr. 2016;70(9):1009–14.
27. Close GL, Russell J, Cobley JN, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2013;31(4):344–53.
28. Close GL, Leckey J, Patterson M, et al. The effects of vitamin D_3 supplementation on serum total 25[OH]D concentration and physical performance: a randomised dose-response study. Br J Sports Med. 2013;47(11):692–6.
29. Dubnov-Raz G, Livne N, Raz R, et al. Vitamin D supplementation and physical performance in adolescent swimmers. Int J Sport Nutr Exerc Metab. 2015;25(4):317–25.
30. Guillemant J, Le HT, Maria A, et al. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. Osteoporos Int. 2001;12(10):875–9.

31. He CS, Fraser WD, Tang J, et al. The effect of 14 weeks of vitamin D_3 supplementation on antimicrobial peptides and proteins in athletes. J Sports Sci. 2016;34(1):67–74.
32. Lewis RM, Redzic M, Thomas DT. The effects of season-long vitamin D supplementation on collegiate swimmers and divers. Int J Sport Nutr Exerc Metab. 2013;23(5):431–40.
33. Nieman DC, Gillitt ND, Shanely RA, et al. Vitamin D_2 supplementation amplifies eccentric exercise-induced muscle damage in NASCAR pit crew athletes. Nutrients. 2014;6(1):63–75.
34. Shanely RA, Nieman DC, Knab AM, et al. Influence of vitamin D mushroom powder supplementation on exercise-induced muscle damage in vitamin D insufficient high school athletes. J Sports Sci. 2014;32(7):670–9.
35. Silk LN, Greene DA, Baker MK, et al. Tibial bone responses to 6-month calcium and vitamin D supplementation in young male jockeys: a randomised controlled trial. Bone. 2015;8(81):554–61.
36. Storlie DM, Pritchett K, Pritchett R, et al. 12-week vitamin D supplementation trial does not significantly influence seasonal 25(OH)D status in male collegiate athletes. Int J Health Nutr. 2011;2(2):8–13.
37. Todd JJ, McSorley EM, Pourshahidi LK, et al. Vitamin D supplementation using an oral spray solution resolves deficiency but has no effect on VO max in Gaelic footballers: results from a randomised, double-blind, placebo-controlled trial. Eur J Nutr. 2016 (**epub**).
38. Wyon MA, Wolman R, Nevill AM, et al. Acute effects of vitamin D_3 supplementation on muscle strength in judoka athletes: a randomized placebo-controlled, double-blind trial. Clin J Sport Med. 2016;26(4):279–84.
39. Huang M, Winters D. Application of ultra-performance liquid chromatography/tandem mass spectrometry for the measurement of vitamin D in foods and nutritional supplements. J AOAC Int. 2011;94(1):211–23.
40. Cashman KD, Fitzgerald AP, Kiely M, et al. A systematic review and meta-regression analysis of the vitamin D intake-serum 25-hydroxyvitamin D relationship to inform European recommendations. Br J Nutr. 2011;106(11):1638–48.
41. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011;59(12):2291–300.
42. McNally JD, Iliriani K, Pojsupap S, et al. Rapid normalization of vitamin D levels: a meta-analysis. Pediatrics. 2015;135(1):e152–66.
43. Black LJ, Seamans KM, Cashman KD, et al. An updated systematic review and meta-analysis of the efficacy of vitamin D food fortification. J Nutr. 2012;142(6):1102–8.
44. Lewis RD, Laing EM, Hill Gallant KM, et al. A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. J Clin Endocrinol Metab. 2013;98(12):4816–25.
45. Gaffney-Stomberg E, Lutz LJ, Rood JC, et al. Calcium and vitamin D supplementation maintains parathyroid hormone and improves bone density during initial military training: a randomized, double-blind, placebo controlled trial. Bone. 2014;68:46–56.
46. Duplessis CA, Harris EB, Watenpaugh DE, et al. Vitamin D supplementation in underway submariners. Aviat Space Environ Med. 2005;76(6):569–75.
47. Gasier HG, Gaffney-Stomberg E, Young CR, et al. The efficacy of vitamin D supplementation during a prolonged submarine patrol. Calcif Tissue Int. 2014;95(3):229–39.
48. Lappe J, Cullen D, Haynatzki G, et al. Calcium and vitamin D supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res. 2008;23(5):741–9.
49. Stockton KA, Mengersen K, Paratz JD, et al. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int. 2011;22(3):859–71.
50. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014;383(9912):146–55.
51. Redzic M, Lewis RM, Thomas DT. Relationship between 25-hydoxyvitamin D, muscle strength, and incidence of injury in healthy adults: a systematic review. Nutr Res. 2013;33(4):251–8.
52. Wyon MA, Koutedakis Y, Wolman R, et al. The influence of winter vitamin D supplementation on muscle function and injury occurrence in elite ballet dancers: a controlled study. J Sci Med Sport. 2014;17(1):8–12.
53. Davey T, Lanham-New SA, Shaw AM, et al. Low serum 25-hydroxyvitamin D is associated with increased risk of stress fracture during Royal Marine recruit training. Osteoporos Int. 2016;27(1):171–9.
54. Davids K, Baker J. Genes, environment and sport performance: why the nature-nurture dualism is no longer relevant. Sports Med. 2007;37(11):961–80.
55. Dubnov-Raz G, Rinat B, Hemila H, et al. Vitamin D supplementation and upper respiratory tract infections in adolescent swimmers: a randomized controlled trial. Pediatr Exerc Sci. 2015;27(1):113–9.