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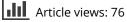
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#### REVIEW

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# A comparison of the effect of supplementation and sunlight exposure on serum vitamin D and parathyroid hormone: A systematic review and meta-analysis

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#### ABSTRACT

**Background:** Supplementation and getting sunlight exposure are two treatments for vitamin D deficiency. However, studies reported conteroversial findings regarding the efficacy of these two methods.

**Objective:** To compare the effect of oral vitamin D supplementation with sunlight exposure on serum vitamin D and parathyroid hormone (PTH).

**Methods:** A computer-based literature search through PubMed, Scopus and Google scholar search engines was conducted until April 2019 to find clinical trials which compared the effect of oral vitamin D supplementation with sunlight exposure on serum vitamin D and PTH. Means for serum 25-hydroxy vitamin D3 (25(OH) D3) and PTH concentration were extracted. A subgroup analysis was used to detect potential sources of inter-study heterogeneity. Mean differences (MD) were analyzed using a random-effects model (the DerSimonian-Laird approach).

**Results:** A total of seven papers were included in the meta-analysis. Pooled analysis showed that vitamin D supplementation significantly elevated levels of serum 25(OH) D3 in comparison with sunlight exposure (MD: 8.56nmol/l, 95%Cl: 4.15, 12.97,  $T^2 = 40.32\%$ ,  $H^2 = 9.45\%$ , P for heterogeneity p < 0.001). Also, the difference between the effect of vitamin D supplementation and sun exposure was lower in studies which used UVB radiation compared with studies which applied direct sunlight (MD: 11.65 nmol/l, 95%Cl: 7.02, 16.28; P for between subgroup heterogeneity = 0.001).

**Conclusion:** Vitamin D supplementation was more effective than sun exposure at increasing serum 25(OH) D3. The difference between efficacy of vitamin D supplementation and sun exposure was lower in studies which used long-term sun exposure or applied UVB treatment instead of direct sunlight.

#### **KEYWORDS**

Supplementation; Sunlight; Vitamin D; Parathyroid Hormone

### Introduction

Vitamin D is a fat-soluble pro hormone with important calciotropic and non-calciotropic actions (Mangge et al. 2015). Hypovitaminosis D is one of the most common nutrient deficiencies prevalent among children and adults (Holick 2017; Holick and Chen 2008). Based on the global assessment, more than 1 billion people across the world are known to suffer from vitamin D deficiency, an issue of considerable importance in the 21st century (Holick 2007). Evidence has suggested that the pathogenesis of several chronic diseases is related to the vitamin D deficiency (Brincat et al. 2015; Guo et al. 2018; Papandreou and Hamid 2015). Therefore, there is no doubt that prevention, evaluation and treatment of vitamin D deficiency can improve community health.

Serum or plasma 25(OH) D3 levels is the most useful biomarker of vitamin D status and vitamin D deficiency is conventionally defined as 25(OH)D3 below 30 nmol/L (Roth et al. 2018). Vitamin D deficiency can be managed by vitamin D supplementation (exogenous vitamin D) or getting regular sunlight exposure (endogenous vitamin D) (Acierno et al. 2006). There are several risk factors for insufficient endogenous synthesis of vitamin D including dark skin (Harris and Dawson-Hughes 1998); limited skin sun exposure (Wicherts et al. 2011) seasonal variation in ultraviolet B (UVB) radiation (Moan et al. 2009) and geographic situations (Chen et al. 2007). Furthermore, genetic variations in vitamin D transporters may affect both endogenous and exogenous vitamin D (Wang et al. 2010). Although consumer attitudes toward vitamin D supplements have increased (Papandreou and Hamid 2015), some researchers advised to get sunlight exposure as a physiological alternative to vitamin D supplementation in sun-rich countries such as India and the Middle East (Papandreou and Hamid 2015).

Several randomized clinical trials were conducted to compare the efficacy of vitamin D supplementation with sun exposure. Some studies showed that oral vitamin D

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supplementation was more effective than sun exposure at increasing serum 25-hydroxy vitamin D3 (25(OH) D3) concentration (Hajhashemi, Khorsandi, and Haghollahi 2017; Lagunova et al. 2013; Patwardhan et al. 2017; Ponda et al. 2017; Wicherts et al. 2011). In contrast, evidence showed that ultraviolet irradiation was as effective as oral vitamin D supplementation (Chel et al. 1998). Also, the effect of duration of treatment and different sources of ultraviolet irradiation are unclear. Present systematic review and metaanalysis was conducted to answer the following questions: 1) what is the difference between the effect of oral vitamin D supplementation and sunlight exposure on 25(OH) D3 and PTH? 2) Whether the duration of treatment and different sources of ultraviolet irradiation can effect on serum vitamin D and PTH?

#### Methods

#### Search strategy

Present study was performed based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Picot et al. 2012). In order to find related articles, a computer-based literature search through PubMed Google scholar and Scopus search engines, was conducted from inception until April 2019. Search strategy was without restriction of language and publication year. We searched databases by using following search terms: ("sunlight"[Mesh] OR "ultraviolet rays"[Mesh] OR "sun exposure"[tiab] OR "sunburn"[Mesh] OR "UV exposure"[tiab] OR "visible light exposure"[tiab] OR "blue light exposure"[tiab]) AND ("cholecalciferol" [Mesh] OR "hydroxycholecalciferol"[Mesh] OR "calcifediol"[tiab] OR "ergocalciferol" [Mesh] OR "calcidiol" [tiab] OR "25-hydroxyvitamin D"[tiab] OR "1,25-dihydroxyvitamin D"[tiab] OR "1α-hydroxyvitamin D"[tiab] OR "1-alpha-hydroxyvitamin D"[tiab] OR "calcitriol"[Mesh] OR "alfacalcidol"[tiab] OR "paricalcitol"[tiab] OR "colecalciferol"[Mesh] OR "vitamin D"[Mesh] OR "vitamin D"[tiab] OR "Ergocalciferols"[Mesh]). An example of a full search strategy including any limits used is displayed in Supplementary Table 1. Moreover, the reference lists of all eligible papers were checked at the final step to find relevant studies not found by initial search. Two authors (SM and FS) separately searched the electronic databases and disagreements were resolved by discussion. Description of population, intervention, comparator and outcome (PICO) is displayed in Supplementary Table 2.

### Inclusion and exclusion criteria

Relevant articles were included if they: 1) compared the effects of vitamin D supplementation with sun light exposure on circulating 25(OH) D3 or parathyroid hormone (PTH); 2) applied a clinical trial design; 3) provided sufficient information on circulating 25(OH) D3 or PTH in treatment groups (e.g., changes in percent of subjects with insufficient serum vitamin D and changes in 1,25 (OH)<sub>2</sub> vitamin D were not appropriate for present study) and 4) conducted on subjects over 18 years of age. Studies were excluded if they: 1) were uncontrolled studies, 2) reported duplicate data; and 3) were reviews, letters, editorial articles, or case reports.

#### Data extraction and quality assessment

Following data were extracted from each article: characteristics of the study (the last name of the first author, publication year and country), study description (design, sample size, type and dosage of intervention in each arm and duration of treatment), methods used to measure 25(OH) D3 and baseline and endpoint values of 25(OH) D3.

#### Quality assessment

Two reviewers (HM and SM) independently evaluated the methodological quality of the eligible studies through Cochrane Collaboration's tool including seven domains: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other sources of bias. Each domain was classified to three categories: low risk of bias, high risk of bias and unclear risk of bias. According to guideline, overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item) or weak (low risk for less than 2 item) (Higgins et al. 2011).

#### Statistical analysis

To calculate the effect size for each outcome parameters, the mean change and its standard deviation (SD) for intervention groups were extracted from each study. A randomeffects model (the DerSimonian-Laird approach) was used to compute weighted mean differences with 95% confidence intervals (Francis et al. 1989). Between-study heterogeneity was tested by Cochran's Q test and quantified by Tauo2  $(T^2)$  and Ho2  $(H^2)$  statistic. To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on study duration (<24 weeks and >24 weeks) and type of sunlight exposure (direct sunlight and UVB radiation). Heterogeneity between subgroups was evaluated using a fixed-effect model. Proportion of the effect size of each study was assessed by sensitivity analysis. Publication bias was not tested because publication bias tests only relevant if you have >10 studies otherwise underpowered to detect much and tend to lead to conclusions that are not justified. We used "metan" to pool mean changes, "metaninf" to run sensitivity analysis and "metabias" to evaluate publication bias. Statistical analysis was performed using STATA 11software (Stata Corp, College Station, Texas, USA).

#### Results

### Literature search results

The process of literature search and screening is presented in Figure 1. Systematic literature search produced a total number of 11,625 publications. Then, we excluded 3740 publications because they were duplicate. Combined search of 3 search engines yielded 7885 unduplicated records. Title and abstract of remained articles were screened based on inclusion and exclusion criteria and 115 records were selected for full text assessment. We excluded 108 studies because they did not compare vitamin D supplementation with sun exposure (n = 87), report insufficient data (n = 18)and other relevant reasons (n = 3). Finally, seven studies were considered eligible for systematic review and meta-analysis (Chel et al. 1998; Hajhashemi, Khorsandi, and Haghollahi 2017; Joh et al. 2019; Lagunova et al. 2013; Papandreou and Hamid 2015; Ponda et al. 2017; Wicherts et al. 2011).

#### **Study characteristics**

Full details of eligible studies are summarized in Table 1. Four studies were conducted in European countries (Chel et al. 1998; Lagunova et al. 2013; Patwardhan et al. 2017; Wicherts et al. 2011), one in Iran (Hajhashemi, Khorsandi, and Haghollahi 2017), one in US (Ponda et al. 2017) and

one in Korea (Joh et al. 2019). Publication date ranged from 1998 to 2019. Mean age varied from 18 to 85 years old. Most of the included studies had a parallel design except for one study used a cross-over design (Lagunova et al. 2013). Four studies were conducted in both genders (Joh et al. 2019; Lagunova et al. 2013; Ponda et al. 2017; Wicherts et al. 2011), two studies recruited women (Chel et al. 1998; Hajhashemi, Khorsandi, and Haghollahi 2017) and one study enrolled men (Patwardhan et al. 2017). Baseline serum 25(OH) D3 ranged from 9.7 to 53.6 nmol/l in the vitamin D group and 9.6 to 50.6 nmol/l in the sunlight group. Vitamin D supplementation dose varied from 400 IU/day to 5000 IU/ day. In the case of sunlight exposure, three studies used UVB radiation (Chel et al. 1998; Norman and Powell 2014; Ponda et al. 2017) and four clinical trials applied direct sunlight (Hajhashemi, Khorsandi, and Haghollahi 2017; Joh et al. 2019; Patwardhan et al. 2017; Wicherts et al. 2011). Duration of intervention ranged from 8 to 48 weeks. Method used to assess serum vitamin D concentration was different among studies: three studies used radioimmunoassay (Chel et al. 1998; Hajhashemi, Khorsandi, and Haghollahi 2017; Wicherts et al. 2011) and the others used Liquid chromatography-mass spectrometry, LIASON automated chemiluminescent immunoassay and ELISA methods (Joh et al. 2019; Lagunova et al. 2013; Patwardhan et al. 2017; Ponda et al. 2017). In addition to serum vitamin D concentration, four studies measured PTH concentration

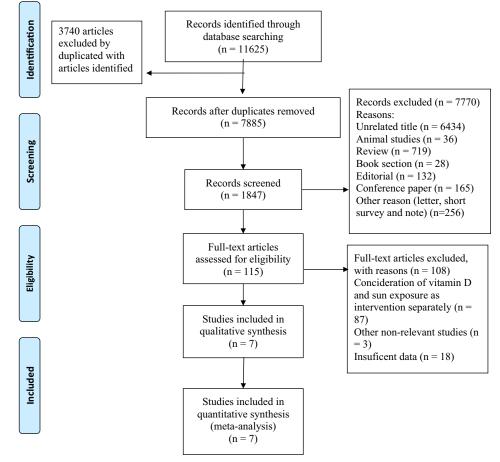


Figure 1. PRISMA flowchart describing systematic literature search and study selection.

Table 1. Description of the studies included in the meta-analysis.	on of the studie	is included in th	ne meta-analysis.							
First author (publication year)	RCT design	Country	Sample Size (Male/ Female); Age	Vitamin D assay	Baseline vitamin D (nmol/l)	Assessed [ outcomes	Duration (weeks)	Vitamin D3 intervention	Sunlight exposure	Results
Chel et al. (1998)	Parallel	Netherlands	N = 45 (0/45) Mean age = 85	Radioreceptor assay	Vitamin D group: 18.78 UVB group: 21.73	25(OH)D3 and PTH	12	Vitamin D3 (400 IU/ per day)	UVB	Vitamin D supplementa- tion is more effective than advised sun- light exposure
Wicherts et al. (2011)	Parallel	Netherlands	N = 211 (53/158) Age = 18-65	Radioimmuno assay	Vitamin D group: 22.1 Sun group: 23.3	25(OH)D3 and PTH	48	Vitamin D3 (800 IU/ per day) Vitamin D3 (1000 IU/	Direct sunlight	Vitamin D supplementa- tion is more effective than advised sun- light exposure
Lagunova et al. (2013)	Cross-over	Norway	N = 31 (53/158) Age = 23-61	Liquid chromatogra- phy-mass spectrometry	Vitamin D group: 53.6 UVB group: 50.6	25(OH)D3	0	Vitamin D3 (2000 IU/ per day)	UVB	The effectiveness of UVB exposure and vitamin D supplementation for increasing serum 25(OH)D3 seems to be dependent on the ini- tial vitamin D status
Ponda et al. (2017)	Parallel	USA	N = 118 (53/65) Age = 18-70	LIASON automated chemiluminescent immunoassay	Vitamin D group: 14 UVB droup: 13	25(OH)D3 and PTH	24	Vitamin D3 (5000 IU/ per day)	UVB	Vitamin D supplementa- tion is more effective than advised sun- licht exnosure
Hajhashemi, Khorsandi, and Haghollahi (2017)	Parallel	Iran	N = 87 (0/87) Mean age = 27	Radioimmunoassay	Vitamin D group: 15.95 UVB group: 15.09	25(OH)D3	10	Vitamin D3 (4000 IU/ per day)	Direct sunlight	Vitamin D supplementa- tion is more effective than sun exposure in increasing 25(OH)D3 in preg-
Patwardhan et al. (2017)	Parallel	N	N = 150 (150/0) Age = 40-60	ELISA	Vitamin D group: 31.9 UVB	25(OH)D3	24	Vitamin D3 (1000 IU/ per day)	Direct sunlight (questionnaire)	Significant increase in 25(OH)D3 was seen in both interven-
Joh et al. (2019)	Parallel	Korea	N = 150 (63/87) Age = 24.4 ± 3.7	Chemiluminescent immunoassay	Vitamin D group: 9.7 UVB group: 9.6	25(OH)D3 and PTH	ø	Vitamin D3 (500 IU/ per day)	Direct sunlight	Significant increase in 25(OHD3 was seen in both interven- tion groups
PTH, parathyroid hormone; UVB, ultraviolet-B.	iormone; UVB, L	ıltraviolet-B.								

(Chel et al. 1998; Joh et al. 2019; Ponda et al. 2017; Wicherts et al. 2011).

Risk of bias assessment based on different quality domains using Cochrane collaboration tool are presented in Table 2. After evaluating the quality of included studies, the quality score of all studies were higher than 2 and classified as good quality.

# Effect vitamin D supplementation on serum 25(OH) D3 concentration compared with sunlight exposure

Six studies provided data on the effect of vitamin D supplementation on serum 25(OH) D3 concentration compared with sun exposure. Pooled analysis showed that vitamin D supplementation significantly elevated levels of serum 25(OH) D3 in comparison with sunlight exposure (MD: 8.56nmol/l, 95%CI: 4.15, 12.97) (Figure 2). Because of a significant between studies heterogeneity ( $T^2 = 40.32\%$ ,  $H^2 = 9.45\%$ , p < 0.001), subgroup analysis was conducted based on duration of intervention and type of sunlight exposure. As shown in Figure 3, the difference between the effect of vitamin D supplementation and sun exposure was similar in

short-term studies (MD: 8.47 nmol/l, 95%CI: 1.34, 15.6) and long-term studies (MD: 8.56 nmol/l, 95%CI: 4.15, 12.97; P for between subgroup heterogeneity = 0.212). Also, the difference between the effect of vitamin D supplementation and sun exposure was lower in studies which used UVB radiation (MD: 3.14 nmol/l, 95%CI: 0.64, 5.64) compared with studies which applied direct sunlight (MD: 11.65 nmol/ l, 95%CI: 7.02, 16.28; P for between subgroup heterogeneity = 0.001) (Figure 4). Sensitivity analysis was performed and overall effect did not change after sequentially excluding one study at a time.

# Effect of vitamin D supplementation on PTH concentration compared with sunlight exposure

The effect of the vitamin D supplementation on PTH was examined in three randomized clinical trials (Chel et al. 1998; Ponda et al. 2017; Wicherts et al. 2011). As illustrated in Figure 5, meta-analysis showed that changes in PTH concentration was not significantly different between vitamin D supplementation and sunlight exposure (MD: 0.12 pmol/l, 95%CI: -0.76, 0.99). Between-study heterogeneity was not

Table 2. Risk of bias assessment for included randomized controlled clinical trials.

Domain	Chel et al. (1998)	Wicherts et al. (2011)	Lagunova et al. (2013)	Ponda et al. (2017)	Hajhashemi, Khorsandi, and Haghollahi (2017)	Patwardhan et al. (2017)	Joh et al. (2019)
Random sequence generation (selection bias)	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	+	?	+	+	+	+
Blinding of participants and personnel (Performance bias)	_	_	_	_	_	_	_
Blinding of outcome assessment (Detection bias)	_	_	_	_	_	_	_
Incomplete outcome data (Attrition bias)	?	+	+	+	+	+	+
Selective reporting (Reporting bias)	?	+	+	+	?	+	+
Other sources of bias	+	+	+	+	?	+	+
Score	3	5	4	5	3	5	5
Overall quality	Good	Good	Good	Good	Good	Good	Good

Author (year)	ES (95% CI) Weight (%)
Wicherts et al (2009)	15.54 (12.45, 18.63) 17.31
Ponda et al (2017)	3.37 (0.42, 6.32) 17.45
Hajhashemi et al (2017)	12.62 (9.32, 15.92) 17.11
Lagunova et al (2013)	- 2.71 (-2.07, 7.49) 15.48
Patwardhan et al (2018)	12.50 (6.01, 18.99) 13.42
Chel et al (1998)	-4.90 (-37.46, 27.66) 1.67
	6.30 (3.47, 9.13) 17.56
Joh et al (2019)	
Overall (I-squared = 87.4%, p = 0.000)	8.56 (4.15, 12.97) 100.00
NOTE: Weights are from random effects analysis	
-37.5 0	37.5



Author (year)		ES (95% CI)	Weight (%
>=24			
Wicherts et al (2009)		15.54 (12.45, 18.63)	17.31
Ponda et al (2017)		3.37 (0.42, 6.32)	17.45
Lagunova et al (2013) -	•	2.71 (-2.07, 7.49)	15.48
Patwardhan et al (2018)	• •	12.50 (6.01, 18.99)	13.42
Subtotal (I-squared = 92.2%, p = 0.000)	$\langle \rangle$	8.47 (1.34, 15.60)	63.66
<24			
Hajhashemi et al (2017)		12.62 (9.32, 15.92)	17.11
Chel et al (1998)		-4.90 (-37.46, 27.66)	1.67
Joh et al (2019)		6.30 (3.47, 9.13)	17.56
Subtotal (I-squared = 77.3%, p = 0.012)	$\langle \rangle$	8.95 (3.00, 14.89)	36.34
Overall (I-squared = 87.4%, p = 0.000)	$\diamond$	8.56 (4.15, 12.97)	100.00
NOTE: Weights are from random effects analysis		I	
-37.5	0	37.5	

Figure 3. The difference between the effect of vitamin D supplementation and sun exposure on serum 25-Hydroxy vitamin D stratified by duration of intervention.

► 15.54 (12.45, 18.63)	17.31
12.62 (9.32, 15.92)	17.11
- 12.50 (6.01, 18.99)	13.42
6.30 (3.47, 9.13)	17.56
<b>11.65</b> (7.02, 16.28)	65.40
3.37 (0.42, 6.32)	17.45
2.71 (-2.07, 7.49)	15.48
-4.90 (-37.46, 27.66)	1.67
3.14 (0.64, 5.64)	34.60
0.56 (4.15, 10.07)	
8.36 (4.15, 12.97)	100.00
	12.62 (9.32, 15.92)   12.50 (6.01, 18.99)   6.30 (3.47, 9.13)   11.65 (7.02, 16.28)   3.37 (0.42, 6.32)   2.71 (-2.07, 7.49)   -4.90 (-37.46, 27.66)

Figure 4. The difference between the effect of vitamin D supplementation and sun exposure on serum 25-Hydroxy vitamin D stratified by type of sunlight exposure.

significant ( $T^2 = 0.12\%$ , H2 = 0.17%, p = 0.416). Sensitivity analysis was carried out and no significant change was observed after removing each study.

### Discussion

Meta-analysis of seven eligible studies revealed that in comparison with sun exposure, oral vitamin D supplementation was more effective at increasing serum 25(OH) D3 concentration. Nevertheless, the difference between efficacy of vitamin D supplementation and sun exposure was lower in studies which applied UVB treatment instead of direct sunlight. Also, there was no significant difference between the effects of vitamin D supplementation and sun exposure on serum PTH concentration.

Vitamin D deficiency is a global health problem and more than one billion vitamin D deficient children and adults have been diagnosed worldwide (Holick 2017; Holick and Chen 2008).Vitamin D deficient individuals have a high risk for chronic diseases (Norman and Powell 2014; Usluogullari et al. 2015). Consumption of vitamin D-rich foods, vitamin D supplementation and getting sun exposure are the most common treatments for vitamin D deficiency (Chel et al. 1998; Hajhashemi, Khorsandi, and Haghollahi

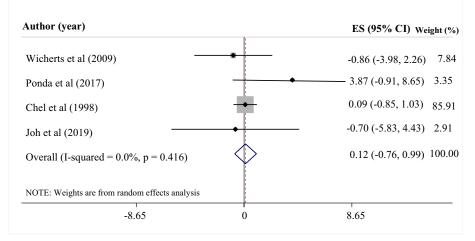


Figure 5. The difference between the effect of vitamin D supplementation and sun exposure on parathyroid hormone.

2017; Ponda et al. 2017). Although the results of studies which compared the efficacy of sun exposure and vitamin D supplementation were inconsistent, present meta-analysis provided a comprehensive quantitative review regarding this topic.

Our results clearly implicated that in comparison with sun exposure, oral vitamin D supplementation was more effective at increasing 25(OH) D3 concentrations. This finding is in agreement with former studies (Hajhashemi, Khorsandi, and Haghollahi 2017; Lagunova et al. 2013; Patwardhan et al. 2017; Ponda et al. 2017; Wicherts et al. 2011). As we know, the vitamin D supplementation considered as the first-line vitamin D deficiency treatment (Wylon et al. 2017). The main advantage of vitamin D supplementation to increase vitamin D in comparison with sunlight has more compliance and makes it a probable therapeutic option in individuals with individuals with problems related liver or kidney (Gupta et al. 2017; Holick 2007). However, another study conducted by Chelet al. (Chel et al. 1998) showed that ultraviolet irradiation is as effective as oral vitamin D supplementation in geriatric patients. In comparison with other studies, the elderly postmenopausal subjects with possible disorders in vitamin D absorption, and in other hands using artificial UVB radiation as more effective source at increasing serum vitamin D may justify differences in findings.

We observed that the efficacy of vitamin D supplementation was more than sunlight even after long-term sun exposure. Approximately, 80–90% of total vitamin D is synthesized in the skin and sun exposure have a key role in endogenous vitamin D synthesis (Holick 2003). However, endogenous synthesis of vitamin D may be influenced by following factors: 1) high melanin concentration in dark skin can filter the UV radiation and decrease the production of vitamin D3 (Harris and Dawson-Hughes 1998); 2) limited skin exposure due to skin-covering clothes (Wicherts et al. 2011) or Hijab in Islamic countries (Hajhashemi, Khorsandi, and Haghollahi 2017); 3) in obese subjects, endogenous vitamin D is slowly released from the skin into blood (Wortsman et al. 2000); 4) in elderly subjects, endogenous synthesis of vitamin D decreases in the skin (MacLaughlin and Holick 1985); 5) seasonal variation in UVB radiation rate has a significant effect on skin produced vitamin D (Moan et al. 2009) and 6) geographic and atmospheric situations can lead to different daily sunlight intensity at similar latitudes (Chen et al. 2007). Therefore, sun exposure may not be always effective and vitamin D supplementation is inevitable in some cases, especially in vitamin D deficient subjects.

Sunlight exposure has both beneficial and harmful effects. In contrast to vitamin D supplementation, endogenous synthesis of vitamin D is a self-regulated and safe process, and has a lower toxicity risk (Holick 2005; Vogiatzi, Jacobson-Dickman, and DeBoer 2014). Therefore, it can be used in high-risk groups including pregnant women and children (Hajhashemi, Khorsandi, and Haghollahi 2017; Vogiatzi, Jacobson-Dickman, and DeBoer 2014). Also, it seems that several advantages of sun exposure are independent of vitamin D synthesis (Weller 2016). Therefore, sun exposure should not be completely replaced by vitamin D supplementation. On the other hand, there are several concerns regarding overexposure of human skin to sun or UVB radiation including sunburn, phototoxic reactions, impaired skin elasticity, increased risk of wrinkling, immune suppression, DNA damage and skin cancer (Contet-Audonneau, Jeanmaire, and Pauly 1999; Gonzalez et al. 1997; Reichrath and Nürnberg 2009). Therefore, sunlight exposure should be recommended with caution and a balance should be achieved and maintained between enough and over exposure to sunlight.

Our study demonstrated that the effect of UVB radiation was more than direct sun exposure on blood 25(OH) D3 concentration. Ultraviolet radiations contribute to less than 1% of total sunlight. Sunlight has two types of ultraviolet radiations including ultraviolet A (UVA) and UVB. In comparison with UVB, UVA has a substantially less biological activity in vitamin D synthesis (Armas et al. 2007; Rajakumar et al. 2007). Artificial UVB radiation is usually provided by fluorescent light bulbs. UVB accounts for 40% of fluorescent light bulb radiation (Acierno et al. 2006). Also, there are several physical barriers that attenuate natural sunlight exposure comprising sunscreens, glass shielding and clothing. These factors can markedly decrease the synthesis of vitamin D3 in the skin (Holick 2006). Therefore, artificial UVB radiation is more effective than sunlight exposure at increasing serum vitamin D.

There are some limitations in our study that should be discussed. Firstly, a significant statistical heterogeneity was detected between studies. However, we tried to find sources of heterogeneity by subgroup analysis. Secondly, the included studies used different tools for measuring serum vitamin D. Although all used methods have acceptable validity and reliability, the effect of these methods on findings should be studied in future. Lastly, the results of the current systematic review and meta-analysis were based on relatively small numbers of studies. Therefore, findings should be interpreted with caution.

The main strength of the current study is that our findings for the first time compare the effect of oral vitamin D supplementation with sunlight exposure on 25(OH) D3 and PTH. In addition, we showed that duration of intervention and type of radiation have important role on efficacy of sun exposure at increasing 25(OH) D3 in comparison with oral vitamin D supplementation.

#### Conclusion

In conclusion, the results of the meta-analysis and systematic review suggested that oral vitamin D supplementation may more effective than sun exposure at increasing serum 25(OH) D3. It seems that, UVB radiation was more effective than direct sunlight exposure at raising serum vitamin D. Artificial UVB radiation may be a good source of vitamin D for prevention of vitamin D deficiency. Therefore, it is suggested that effect of UVB radiation from artificial sources should be given more attention for future studies. Future prospective randomized clinical trials are warranted to obtain more precise conclusion. Moreover, for future metaanalyses it is recommended that the analysis should be repeated based on individual patient data (IPD) meta-analyses.

#### Abbreviations

25(OH) D3	25-hydroxy vitamin D3
MD	mean difference
PTH	parathyroid hormone
UVA	ultraviolet A
UVA	ultraviolet B

#### **Disclsosure statement**

No potential conflict of interest was reported by the authors.

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