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Oral health and vitamin D in adult: a systematic review

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Abstract

This systematic review aimed to provide a synthesis of the evidence relating to how the provision of vitamin D supplements influences oral health status. An electronic database search was performed across six databases using a standardised search strategy. The PICO framework (Population, Intervention, Comparison, Outcome) was used to define the review question. The screening and selection followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses process (PRISMA). The quality of reporting was assessed using Consolidated Standards of Reporting Trials (CONSORT) guidelines, and the bias was assessed using the revised Cochrane tool RoB2. A total of 1812 studies were retrieved. 1427 studies were excluded due to unmet inclusion criteria. Full texts of seventy-five potential studies were retrieved and ultimately six studies met the inclusion criteria. There were limitations in the quality of reporting of studies (between 49 % and 73 %). 70 % of the risk of bias items were in the low risks category. Vitamin D interventions varied with respect to dosage and duration. Qualitative syntheses identified significantly better oral health outcomes. Heterogeneity of study design, intervention and outcomes precluded quantitative synthesis. Few clinical trials investigated the effect of vitamin D supplementation on oral health. There is considerable heterogeneity among studies interventions and oral health outcomes. Quality of reporting of studies has limitations and there is evidence of study biases. Nonetheless, qualitative synthesis of the evidence suggests that vitamin D supplements improve oral health outcomes, particularly periodontal health. Calcium may also play a significant role. Further high-quality trials are required of comparable vitamin D supplements with similar oral health outcomes focused to inform quantitative synthesis of the evidence.

Key words: **Oral health: Vitamin D: Review: Randomised clinical trial**

Vitamin D is a fat-soluble vitamin derived from endogenous production in the skin that can be obtained either from the diet or by exposure to ultraviolet B from sunlight with a wavelength of 290–315 nm[1]. The active form of vitamin D is calcitriol or 1, 25-dihydroxyvitamin D3 (1,25(OH)2D3). Vitamin D is essential for optimal intestinal calcium (Ca) absorption to support the regulation of Ca homeostasis for bone health and phosphorus metabolism[2]. Vitamin D also has a role in inflammatory response and influences immunity at various stages, such as antibacterial response, antigen presentation and regulation of adaptive and innate immunity[3].

Vitamin D intake is reported to be associated with oral health status such as periodontal conditions[4], oral cancer[5], tooth mineralisation[6] and tooth loss[7]. Vitamin D receptor play an important role in maintaining oral health, as it is also reported to be associated with periodontal disease progression[4]. Mostly periodontal status has been assessed by bleeding on probing (BOP), pocket depth (PD), gingival bleeding, clinical attachment loss (CAL) and alveolar bone loss. Vitamin D along with Ca are considered as one of the important factors in ensuring good oral health[8]. Studies also reported that those with high vitamin D serum level had lower number of teeth with periodontal pockets[9], decreased risk of tooth loss[7] and better periodontal conditions[10].

In addition, a systematic review on clinical controlled trials that were conducted on children reported that vitamin D supplement was associated with a reduced risk of caries among the children[11]. There are a significant number of cross-sectional studies about oral health and vitamin D among the adults' population. However, there is no systematic review of clinical trials was conducted on adults with regards to the vitamin D supplements and oral health. Therefore, this comprehensive review aimed to explore clinical trial data about the effect of vitamin D on oral health among the adult population.

Abbreviations: BOP, bleeding on probing; CONSORT, Consolidated Standards of Reporting Trial; GI, gingival index; PD, pocket depth.

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Methodology

Information sources and search strategy

An electronic database search was performed using PUBMED, World of Science, Scopus, The Cochrane Library, OVID, Proquest and Ebcohost. There was no limit on the date retrieved and it was based on the databases that have a link with the institutions. The PICO model was used to define the review questions. The population group of this review was adults, and the Interventions were related to vitamin D administration. The comparison was placebo or control intervention group(s), and the outcomes measures were oral health parameters.

The search terms were based on and adapted from previous reviews related to vitamin D and oral health[11–13]. The related MESH words were also used in the search. The keywords for vitamin D were vitamin D OR plasma vitamin D OR 25-hydroxy vitamin D OR plasma vitamin D OR 25-hydroxycholecalciferol OR 25hydroxyergocalciferol OR calcidiol OR calcifediol OR ergocalciferol OR cholecalciferol OR calciferol OR 25-hydroxycholecalciferol vitamin D OR 25-hydroxycholecalciferol vitamin D3 OR 25-hydroxyvitamin D OR 25-hydroxyvitamin D3 OR 25(OH)D OR 25(OH)D3 OR 1,25(OH)2D OR 25-hydroxyvitamin D. Meanwhile, the keywords used for oral health were broader, to ensure its cover most of the related area. Examples of the keywords used in the search were dental health OR oral health OR dental hygiene OR mouth diseases OR oral cancer OR plaque control OR dental deposit OR periodontal pocket OR oral mucositis OR dry mouth OR facial pain OR halitosis. Related articles from reference lists were manually searched for potential papers that met inclusion criteria.

Study screening and selection

All the titles retrieved from the search were screened by two reviewers (NAM and KM). If there was a doubt regarding the title, the abstract was read. If there was disagreement between the two reviewers, discussion and consensus was achieved with a third reviewer (NR). Potentially relevant articles related to the vitamin D and oral health were included for further screening. Duplicated papers were identified and removed. The titles and type of studies were grouped accordingly. The inclusion criteria for the search were randomised controlled trials studies relating to both 'Vitamin D intervention (s)' and 'oral health'. Studies performed on animals, review papers and those not in the English language were not selected for this review. Following this, the full texts of the effective articles were retrieved and analysed. Data were extracted based on: (i) study profile (such as year and country of the study, study setting and sample size), (ii) method of assessment and outcome(s), (iii) intervention (mode, dosage, frequency, duration and additional intervention) and (iv) key findings (Table 1).

Data items

For each study, information on the oral assessments indicators and vitamin D were retrieved. The oral assessments included were (i) periodontal conditions, (ii) bone loss or bone gain and (iii) tooth retention. The vitamin D levels and dosage were also obtained from each study. The measurement was standardised to the International Unit (μg) or USA Pharmacopeia (USP).

Study quality and risk of bias assessment

The studies quality ('quality of reporting') was assessed and quantified using the Consolidated Standards of Reporting Trials (CONSORT) checklist[14]. The studies were rated across twenty-five items. The studies' risk of bias was assessed using the Cochrane revised tool for assessing the risk of bias in randomised trials (RoB 2)[15]. The following parameters were used to assess the bias: (i) randomisation process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of outcome and (v) selection of the reported result.

Synthesis of vitamin D effectiveness

Qualitative synthesis of interventions in terms of (i) serum vitamin D levels, (ii) dental plaque levels (oral hygiene and plaque index scores), (iii) gingival health status (bleeding on probing (BOP) and gingival index (GI) scores), (iv) periodontal PDs, (v) clinical attachment loss (CAL) is a distance from the cemento-enamel junction to the bottom of clinical pocket, (vi) bone attributes- alveolar bone levels, infrabony defects and bone loss and (vii) others – number of dental caries and periodontal inflamed surface area scores. Quantitative synthesis was not employed because of heterogeneity among studies in terms of vitamin D intervention and in terms of the outcome of studies.

Results

A total of 1812 studies were identified from the initial search. Duplicated studies were identified and removed (n 310). Two independent reviewers screened all the remaining studies (n 1502). Following this, 1427 studies were excluded due to unmet inclusion criteria (45 were animal/laboratory-based studies, 16 were review papers and 1366 not related to vitamin D interventions relating to oral health). Full texts of the seventy-five potentially effective studies were retrieved and screened by two independent reviewers for eligibility. The seventy studies were excluded because one study was a review, three studies were laboratory, sixteen studies were not related to 'Vitamin D and oral health', eighteen studies were excluded because of age (studies among children aged ≤ 18) and thirty-two studies were excluded because of study design (twenty-one cross-sectional studies, eight case study and three cohort studies). One additional study was identified through the reference linkage from the reference lists of studies screened. Finally, six 'effective studies' met the inclusion criteria to inform this review and synthesis of the studies' findings was performed. The study screening and selection process was summarised in Fig. 1 (PRISMA flow diagram of the screened articles). Table 1 describes the details of the six papers that met the inclusion criteria.

Studies characteristics

Among the six studies, five studies were published between the year 2001 and 2017[16–20]. The study from the reference linkage was published in 1979[21]. Half (50·0 %, n = 3) of the studies were

Table 1. Details of the studies

Author, year and country	Study setting	Sample size (drop out rate)	Instruments	Study outcome(s)	Intervention(s)	Duration of study	Findings
Woelbar, J. P. *et al.* 2017 (Pilot), Germany	Clinic (Operative and Periodontology departments) – min age 23-year-old – max age 70-year-old	Recruited:16 – Test (11) – Control (5) Completed: 15 – Test (10) – Control (5) Drop out %: 6·25	– Oral assessment (BOP, GI, PI, PD, CAL, PISA) – Food diaries – BMI	Primary outcome – Bleeding on probing (BOP) Secondary outcomes: – Gingival Index (GI-Loe and Silness) – Plaque index (PI-Silness and Loe) – Full mouth probing depths (PD) -Clinical attachment level (CAL-six sites of the teeth) – Periodontal inflamed surface area (PISA)	Test Mode: Tablet vitamin D supplement Dosage: 500 µg (12·5 µg) Frequency: Daily Duration: 8 weeks Additional intervention – Sun exposure for 15 min. – Low cab. diet (< 139g/d) – Daily intake of *n*-3 fatty acid – Daily intake of vitamin C (e.g. fruits) – Daily intake of vitamin D (sun exposure for 15 min. with supplements of 500 µg (12·5 µg)) – Daily intake of antioxidant (e.g. berries) – Daily intake of fibers (e.g. vegetables) – delivered verbally for 30 min and information brochure on recommended and restricted diet. – were required to fill out a daily food diary Control – continue their dietary habits	8 weeks	The measured parameters were significantly reduced in the test group compared to the control group, with optimised diet (rich in *n*-3 fatty acids, vitamin C and D, antioxidants and fibre) and without any changes in oral hygiene performance*. Baseline and 8 weeks BOP (%) ($P < 0·05$)* Test = 53·57 ± 18·65 – 24·17 ± 11·57 Control = 46·46 ± 15·61 – 64·06 ± 11·27 GI scores (mean) ($P < 0·01$)* Test = 1·10 ± 0·51 – 0·54 ± 0·30 Control = 1·01 ± 0·14 – 1·22 ± 0·17 PI scores (mean) ($P > 0·05$) Test = 0·88 ± 0·48 – 0·84 ± 0·47 Control = 0·81 ± 0·46 – 0·97 ± 0·70 PD scores (mean) ($P > 0·05$) Test = 2·19 ± 0·34 – 2·11 ± 0·35 Control =2·31 ± 0·52 – 2·22 ± 0·47 CAL scores (mean) ($P > 0·05$) Test = 2·31 ± 0·52 – 2·22 ± 0·47 Control = 2·53 ± 0·90 – 2·76 ± 0·88 PISA scores (mean; mm^2) ($P < 0·001$)* Test = 6·38·88 ± 305·41 – 2·84·83 ± 174·14 Control = 661·24 ± 420·05 – 963·24 ± 373·78
Khan F.R. *et al.* 2016, Pakistan.	Community (Centre for pregnant women - gestational age of 12–16 weeks) – min age 26-year-old – max age 32-year-old	Recruited:86 – Test (43) – Control (43) Completed: 85 – Test (36) – Control (49) For birth weight only – Test (27/36) – Control (36/49) Drop out %: 1·16	– Oral assessment (BOP, PD, CAL, DMFT) – Blood samples (serum level of vitamin D)	– Low birth weight (< 2500 g) – Periodontal disease (two sites with attachment loss (CAL ≥ 2 mm) or PD ≥ 3 mm)	Test Mode: Oral syrup vitamin D supplement. Dosage: 4000 µg Frequency: Daily Duration: 6 months Additional intervention – none. Control Mode: Oral syrup of placebo. Dosage: - Frequency: Daily Duration: 6 months Both groups received	6 months	Baseline and 6 months Vitamin D ($P > 0·05$). vitamin D level improved in the test group and reduced in the control group from baseline to 6 months but there were no significant differences. Test 12·9 ± 6·3 ng/ml - 15·36 ng/ml ± 7·62 Control 12·7 ± 5·3 ng/ml – 11·3 ± 4·7 ng/ml Periodontal ($P > 0·05$). Improvement in periodontal status among the groups but there was no significant difference from baseline to 6 months. PD ($P > 0·05$) Test = 1·83 ± 0·5 mm – 1·72 ± 0·52 mm

Table 1. (*Continued*)

Author, year and country	Study setting	Sample size (drop out rate)	Instruments	Study outcome(s)	Intervention(s)	Duration of study	Findings
					standardised oral hygiene education*		Control = 1·81 ± 0·6 mm - 1·76 ± 0·60 mm CAL($P > 0·05$). Test = 1·2 ± 0·9 mm – 0·86 ± 0·80 mm Control; = 1·0 ± 0·85 mm – 0·98 ± 0·91 mm At 6 months Vitamin D ($P < 0·01$) There was a significant difference between the groups at 6 months in vitamin D levels. Test = 15·36 ± 7·62 ng/ml Control = 11·3 ± 4·7 ng/ml Periodontal ($P > 0·05$) There was no significant difference between the groups at 6 months in PD and CAL. PD ($P = 0·79$) Test = 1·72 ± 0·52 mm Control =1·76 ± 0·60 mm CAL ($P = 0·35$) Test = 0·86 ± 0·80 mm Control = 0·98 ± 0·91 mm Low birth weight (LBW) ($P > 0·05$) LBW ($P = 0·26$) Test = 2·80 ± 0·52 kg Control = 2·98 ± 0·73 kg
Hiremath V. P. 2013, India	Clinic (Dental College) – min age 18-year-old – max age 64-year-old	Recruited:96 4 groups (*n* 24) 452 people screened* Completed: 88 Drop out %: 8·33	– Oral assessment (GI) – blood samples (serum level of vitamin D)	– GI, – Serum vitamin D (25-hydroxyvitamin.D)	Randomly Mode: Oral tablets vitamin D supplement. Dosage: i) 2000 μg (code A) ii) 1000 μg (code B) iii) 500 μg (code C) iv) placebo (code D) Frequency: Daily Duration: 3 months Additional intervention - none.	3 months	Increased dose is directly proportional with increased vitamin D level in serum. Vitamin D is a safe and effective anti-inflammatory agent in doses ranging from 500 μg to 2000 μg*. Vitamin D There were significant differences in vitamin D serum level between the groups at baseline and 90 days ($P < 0·001$) A = 22·47 ± 6·98 ng/ml – 52·20 ± 10·17 ng/ml B = 26·80 ± 0·68 ng/ml – 43·68 ± 8·80 ng/ml C = 23·98 ± 5·05 ng/ml – 36·82 ± 6·13 ng/ml Baseline and 90 days Vitamin D ($P < 0·001$) There were significant increases in vitamin D serum level monthly among the groups A = 9·9116 ng/ml per month ($P < 0·001$) B = 5·6238 ng/ml per month ($P < 0·001$) C = 4·2743 ng/ml ($P < 0·001$) There was no significant increase monthly

Table 1. (*Continued*)

Author, year and country	Study setting	Sample size (drop out rate)	Instruments	Study outcome(s)	Intervention(s)	Duration of study	Findings
							in group D = 0·1156 ng ml ($P > 0·05$)* Baseline and time point GI There was a significant reduction in GI scores in group A, B and C from baseline to the time point A ($P < 0·0001$) Baseline = 2·41 ± 0·54 30 days = 1·77 ± 0·63 B ($P < 0·0001$) Baseline = 2·39 ± 0·57 60 days = 1·16 ± 0·71 C ($P < 0·0001$) Baseline = 2·24 ± 0·46 90 days = 1·43 ± 0·71 There was no significant difference in GI scores of group D from baseline to the time point D ($P > 0·05$) Baseline = 2·23 ± 0·61 90 days = 1·89 ± 0·64
Bashutski J. D, *et al.*2011, (Pilot) USA	Clinic (University-Patients with severe periodontal disease) – min age 30-year-old – max age 65-year-old	Recruited:40 4 groups -based of vitamin D level A-vitamin D deficient (< 20 ng.mL) with placebo (*n* 7) B-vitamin D sufficient with placebo (*n* 13) C- vitamin D deficient with test (*n* 4) D- vitamin D sufficient with test (*n* 16) Completed: 40 Drop out %: 0	– Oral assessment (BOP, PD, CAL) – radiographic evaluation (BW and periapical) – blood samples for vitamin D level (25(OH)D	– Infrabony defect resolution at bone side following periodontal surgery (clinical and radiographic using linear defect resolution = from deepest point of the initial defect to the first point at which complete bone fill occurred)	Test Mode: Oral vitamin D supplement Dosage: 800 μg Frequency: Daily Duration: given 3 days before the surgery and continued for 6 weeks additional intervention – subcutaneous injection of teriparatide – 1000 mg Ca oral supplement Control Mode: oral vitamin D supplement Dosage: 800 μg Frequency: Daily Duration: given 3 days before the surgery and continued for 6 weeks additional intervention – subcutaneous injection of placebo – 1000 mg Ca oral supplement	1 year	Within-test groups There were significant improvement in linear bone, PD and CAL in the vitamin D sufficient compared with the vitamin D deficient in the test group. There was no significant difference in BOP between the groups at 12 months. Baseline and time point vitamin D sufficient had more radiographic linear bone gain compared with vitamin D deficient($P = 0·03$). 6 months = 1·10 mm *v.* 0·20 mm 9 months = 1·50 mm *v.* 0·40 mm 12 months = 2·05 mm *v.* 0·87 mm Vitamin D sufficient had greater CAL gain compared with vitamin D deficient at 6 months ($P < 0·01$). 6 months = 1·25 mm *v.* 0·40 mm Vitamin D sufficient had greater PD reduction compared with vitamin D deficient ($P < 0·01$) 3 months = 2·75 mm *v.* 1·20 mm, 6 months = 2·90 mm *v.* 1·30 mm 9 months = 2·70 mm *v.* 1·20 mm At 12 months BOP reduced in vitamin D sufficient

Table 1. (*Continued*)

Author, year and country	Study setting	Sample size (drop out rate)	Instruments	Study outcome(s)	Intervention(s)	Duration of study	Findings
					Placebo medication - not mentioned specifically*		(36 %, $P < 0{\cdot}01$) and increased in vitamin D deficient (12 %, $P < 0{\cdot}01$) at 12 months. There was no significant improvement on CAL gain and PD reduction in vitamin D sufficient and vitamin D deficient at 12 months CAL = 1·54 mm *v.* 1·75 mm PD = 2·57 mm *v.* 1·88 mm Within-control groups There were minimal changes of linear infrabony defect at all time-point with no significant different ($P > 0{\cdot}05$) At 12 months There were significant improvement in CAL gain and PD reduction in vitamin D sufficient compared with vitamin D deficient at 12 months ($P < 0{\cdot}01$). CAL = 0·92 mm *v.* – 0·43 mm PD = 1·83 mm *v.* 0·43 mm BOP reduced in both groups but no significant differences between groups; 36 % in vitamin D deficient and 42 % in vitamin D sufficient at 12 months ($P > 0{\cdot}05$)
Krall. E. A. *et al.* 2001, USA	Clinic Health subjects from clinical trial of osteoporosis – min age 67-year-old – max age 77-year-old	Recruited: 145 (295 followed over the 5 years' period) Test – 82 Control - 63 Completed: 145 Drop out %: 0	– Oral assessment (caries tooth, tooth loss, periodontal disease-PD > 3·5 mm) – Questionnaire (baseline to 3 years regarding tooth loss) – Questionnaire of food frequency for dietary Ca and vitamin D intakes every 6 months	Tooth loss	Test Mode: Oral tablet of vitamin D suppl. Dosage: 700 μg Frequency: Daily Duration: 3 years Additional intervention – Daily calcium citrate malate (500 mg/d) Control Mode: Oral tablet of placebo (containing microcrystalline cellulose) Dosage: same no. of pills as test group Frequency: Daily Duration: 3 years Additional intervention – Daily placebo (same no. of pills of test group for calcium citrate)	5 years (with 2 years observational study)	Baseline and 3 years There was a significant difference between the groups for tooth loss ($P = 0{\cdot}04$) Test: 13 % loss Control: 27 % loss Fourth and fifth years (observational stage) There were no significant differences between the test and control groups at the end of the follow-up in parameters below. -caries ($P = 0{\cdot}18$) -oral hygiene ($P > 0{\cdot}05$) -periodontal disease (0·92)

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Table 1. (*Continued*)

Author, year and country	Study setting	Sample size (drop out rate)	Instruments	Study outcome(s)	Intervention(s)	Duration of study	Findings
Wical, K.E. & Brussee, P.,1979, USA	Clinic (Prosthodontic clinic - Patient who had undergone extraction and immediate placement of denture) – min age 39-year-old - max age 79-year-old	Recruited: 60 Completed: 46 Test – 23 Control – 23 Drop out %: 23	– Radiographic examination – panoramic of jaw (before extraction, few days after, 3-month and 1 year) – Records of 7 days' dietary diet (amount and ratio of Ca and phosphorus)	Bone loss of the alveolar bone per extraction	Test Mode: Oral tablet of vitamin D_2 Dosage: 375 USP Frequency: Daily Duration: 1 year Additional intervention –750 mg of calcium carbonate Control Mode: Oral tablet of placebo (lactose and methyl cellulose) Dosage: - Frequency: Daily Duration: 1 year Additional intervention -placebo tablets	1 year	Baseline and 12 months There was a significant difference in bone loss per extraction between the groups ($P < 0{\cdot}005$) Test (n 23) = 12·7 mm^2 (SD 5·2) Control (n 23) = 19·8 mm^2 (SD 8·3) There was a significant difference in bone loss per extraction for maxillary arch between the groups ($P < 0{\cdot}01$) Test (n 20) = 11·8 mm^2 (± 5·9) Control (n 20) = 17·6 mm^2 (± 6·8) There was a significant difference in bone loss per extraction for mandibular arch between the groups ($P < 0{\cdot}025$) Test (n 23) = 13·6 mm^2 (± 5·7) Control (n 23) = 22·2 mm^2 (± 12·9)

BOP, bleeding on probing; CAL, clinical attachment loss; PD, pocket depth.

performed in the USA[19–21], one in Europe (Germany)[16] and two studies in Asia (Indian and Pakistan)[17,18]. Most studies were performed in the clinical (dental) setting (83·3 %, n = 5)[16,18–21], and one study was a community-based study among pregnant women[17]. These six trials involved a total of 419 participants out of 443 recruited participants. The dropout rate ranged from approximately 0 %[19,20] to 23 %[21]. Test group (vitamin D intervention) sample size ranged from 11[16] to 82[20]. Control group sample sizes ranged from 5[16] to 63[20]. Duration of the studies varied: 8 weeks[16], 3 months[18], 6 months[17], 12 months[19,21] and 5 years[20]. The age of the subjects ranging from minimum of 23 years old to maximum age of 79 years old.

The studies involved investigations on the effects of vitamin D supplementation on the periodontal status[16–18], alveolar bone loss[19,21] and tooth retention[20], as well as the vitamin D serum levels[17,18]. The type of subjects varied among the studies, namely dental patients with gingivitis[16], pregnant women[17], subject from dental college clinic (did not specify the type of clinic)[18], patients with severe periodontal disease scheduled for open flap debridement surgery[19], healthy adults with bone loss from the hip study[20] and patients who had undergone extraction for an immediate denture[21].

Study intervention(s)

All patients in the experimental group received supplementation of vitamin D but of different dosages and of different types of delivery modes; modified diet with 500 μg vitamin D and sun exposure of 15 min[16], 4000 μg vitamin D supplement daily[17], 2000 μg, 1000 μg and 500 μg of vitamin D daily[18], subcutaneous injection of teriparatide (20 μg) with Ca (1000 mg) and vitamin D oral supplements (800 μg)[19], vitamin D (≥ 400 μg/d) and Ca (≥ 1000 mg/d) supplement, Ca (500 mg/d) and vitamin D (700 μg/d)[20] and 750 mg of calcium carbonate and 375 μg units of vitamin D[21].

In two-third of the studies (66·6 %, n = 4), the control groups received placebo tablets (typically microcrystalline cellulose and lactose)[17,18,20,21]. In one study, the control group was assigned to follow their usual diet (unmodified)[16]. Meanwhile, in the study of Bashutski *et al.*[19], both the experimental and the control groups were given the same vitamin D supplements (and of similar dose) but the control group received a placebo subcutaneous injection whereas the test group received teriparatide injection.

Outcome measures

The primary outcomes for the studies were bleeding on probing[16], periodontal disease[17], GI and serum vitamin D level[18], infrabony defect[19], tooth loss[20] and alveolar bone loss[21]. Three of the studies used clinical oral indicators and blood samples serum of vitamin D[17–19], and the other studies used oral assessment with either a radiographic assessment[19,21] or a questionnaire[20]. The questionnaire was related to tooth loss[20] and/or daily diet[16,20]. One study used three parameters; oral indicators, blood samples and radiographic assessment[19]. The oral indicators that were commonly used were the bleeding on probing, GI, plaque index, probing depth and clinical attachment loss. Other oral indicators were alveolar bone loss, periodontal inflamed surface area (PISA), DMFT (Decay, Missing, Filled, Teeth) and tooth loss.

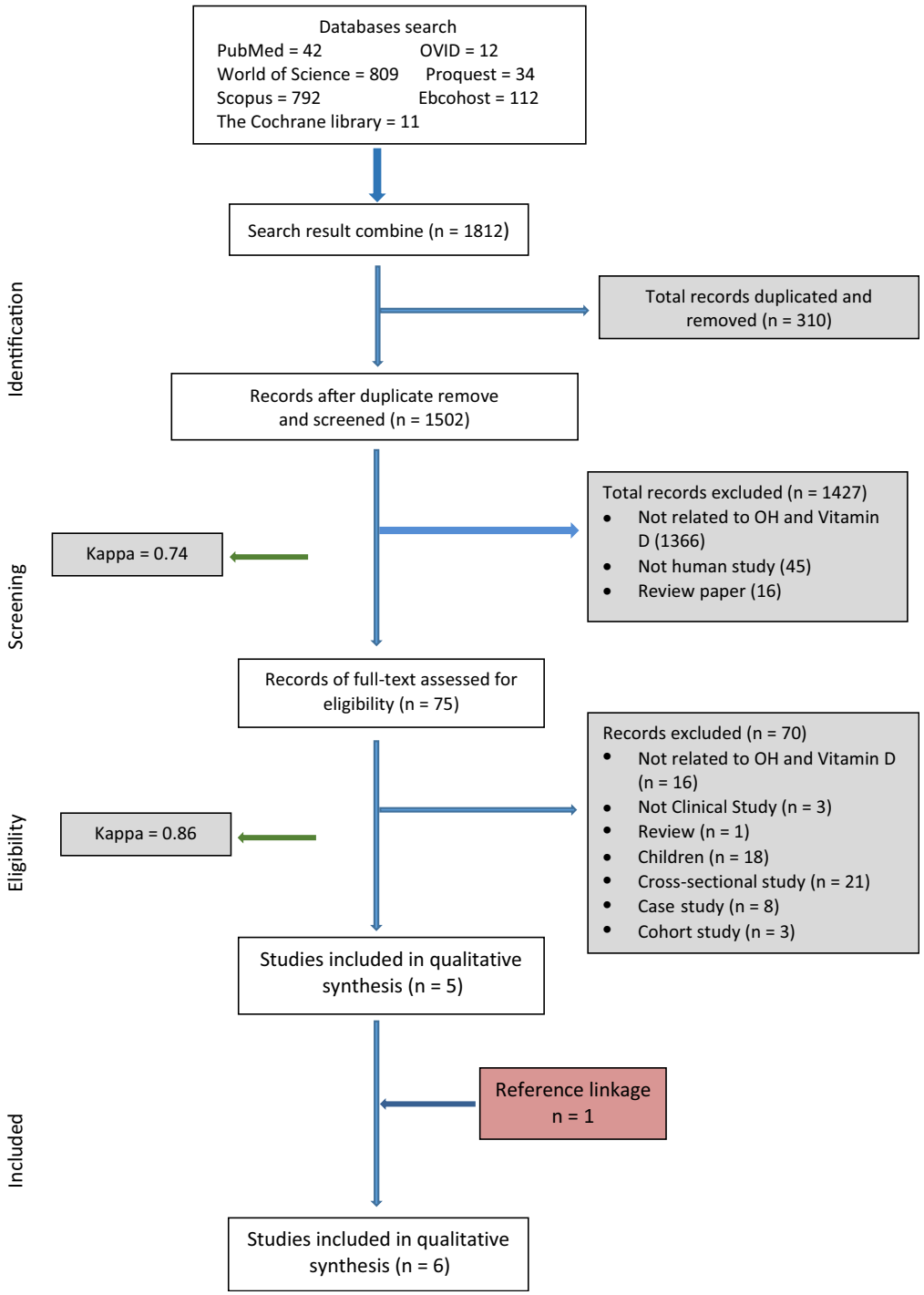

Fig. 1. PRISMA flow of the review process.

Synthesis of results

Periodontal conditions

(i) Bleeding on probing. Two studies assessed the bleeding on probing (BOP) status[16,19]. Both studies reported a significant reduction of BOP at the end of the study. In one of the studies, subjects were given 500 μg vitamin D daily, along with sun exposure and other dietary intake changes - significant difference between the test and control group were observed ($P < 0{\cdot}05$)[16]. The other study reported that within the test groups, a significant reduction was observed in the BOP at 12 months, ranging from 12 % to 36 % for vitamin D deficient ($P < 0{\cdot}01$) and vitamin D sufficient ($P < 0{\cdot}01$) supplied with 800 μg vitamin D supplements[19]. However, there was no significant difference in BOP between the groups. Whereas in the

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control groups, a reduction in BOP was observed but there were no significant difference between and within the groups at the end of 12 months.

(ii) gingival index. Two studies assessed GI scores[16,18]. Both studies showed a significant reduction in the GI scores. The subjects were given 500 μg vitamin D daily, were exposed to sun exposure and given other dietary intake changes - significant difference between the test and control group were observed ($P < 0{\cdot}01$)[16]. Meanwhile, the other study demonstrated a significant improvement in the GI score for all test groups that received vitamin D supplements. All dosage 500 μg, 1000 μg and 2000 μg showed significant reduction after 90 days ($P < 0{\cdot}001$) compared with the placebo group ($P > 0{\cdot}05$). In addition, the serum vitamin D levels were significantly increased monthly in all experimental groups. The anti-inflammatory effects were seen earlier with a higher dosage of Vitamin D. The experimental group with the highest dosage of vitamin D supplementation, i.e. 2000 μg had a mean serum level increased of ~10·0 ng/ml ($P < 0{\cdot}001$) and a mean change of GI scores of –0·63 ± 0·09 after 30 d. Meanwhile, the other groups with vitamin D supplementation of1000 μg had a mean serum level increased of ~5·6 ng/ml ($P < 0{\cdot}001$) and a mean change of GI scores of –0·38 ± 0·01, and 500 μg had a mean serum level increased of ~4·3 ng/ml and a mean change of GI scores of –0·28 ± 0·01 after 30 days. The increased dose of vitamin D was directly proportional to the serum vitamin D level and to lower GI scores.

(iii) plaque index. One study assessed the plaque index scores[16], however no significant difference was observed between the test and control group ($P > 0{\cdot}05$). There was also no significant difference within the test group (a minimal reduction occurred with mean scores: 0·88 ± 0·48 to 0·84 ± 0·47), while increased plaque index scores were observed in the control group.

(iv) pocket depth. Three studies assessed the PD[16,17,19]. All studies showed a reduction in PD scores, but the changes were not significant at the end of study, between the test and control group in two studies[16,17]. A reduction was observed in one study from baseline to 6 months, but there were no significant differences[17]. Another study showed significant reduction within the test groups, with vitamin D sufficient having greater PD reduction than the vitamin D deficient ($P < 0{\cdot}01$) at all time points (3 months, 6 months and 9 months). There was no significant reduction observed between the groups at 12 months. Meanwhile, within the control groups, no significant difference was observed between the groups at all time points ($P > 0{\cdot}05$). A significant reduction was observed in vitamin D sufficient compared with vitamin D deficient at 12 months ($P < 0{\cdot}01$)[19].

(v) Clinical attachment loss. Three studies assessed clinical attachment loss[16,17,19]. There was no significant improvement observed in two of the studies, either between the groups or within the groups[16,17]. One study showed significant clinical attachment loss gain in vitamin D sufficient group compared with the vitamin D deficient group at 6 months ($P < 0{\cdot}01$), but there was no significant improvement at 12 months between the groups ($P > 0{\cdot}05$). However, within the control groups, there was a significant improvement of clinical attachment loss at 12 months in vitamin D sufficient compared with the vitamin D deficient ($P < 0{\cdot}01$).

(vi) periodontal inflamed surface area. One study assessed the periodontal inflamed surface area score[16]. Vitamin D dosage of 500 μg daily with sun exposure and other dietary intake changes reported a significant difference between the test and control group at the end of the study ($P < 0{\cdot}001$). The test group inflammation area was reduced significantly, while the control group inflammation area increases at the end of the study.

Tooth loss

One study assessed the number of teeth lost[20]. The subjects were given 700 μg vitamin D daily for 3 years, in combination with calcium citrate (500 mg) daily. There was a significant difference in tooth loss between the test and control group at three years ($P < 0{\cdot}05$); the prevalence of tooth loss in the test group was 13 % and 27 % in the control group. Although there was a significant difference in tooth loss between the groups at follow-up, only Ca intake was significantly associated with odds of tooth loss during follow-up (OR = 0·5; 95 % CI:0·2, 0·9, $P < 0{\cdot}05$). The Ca and vitamin D supplements were associated with a lower risk of tooth loss in older adults and women (OR 0·4; 95 % CI: 0·2, 0·9; $P < 0{\cdot}05$). The control group (without the Ca and vitamin D supplements) lost one or more teeth compared with the test group during the study.

Alveolar bone loss

Two studies assessed the alveolar bone loss using radiographic assessment following periodontal surgery[19] and tooth extraction[21]. Both studies showed that Ca and vitamin D helps to reduce the process of bone loss following the extraction with increased bone gain after periodontal surgery. The differences between the groups in both studies were still significant at follow-up assessment of 12 months. One study showed that within the test group, the vitamin D sufficient, there was significant radiographic linear bone gained compared with vitamin D deficient at 6 months, 9 months and 12 months ($P < 0{\cdot}05$). However, no significant difference changes were observed at all time points within the control groups. While the other study showed a significant reduction in bone loss following extraction of teeth and immediate denture placement in the test group compared with the control group ($P < 0{\cdot}01$). The participants in the test group were given 750 mg of Ca and 375 USP (or μg) units of vitamin D. The bone loss in the experimental group was less compared with the control group; 12·7 ± 5·2 mm^2 and 19·8 ± 8·3 mm^2, respectively. The percentage of the difference between the test and control group was 39 % less bone resorption in the mandible and 32 % less bone resorption in the maxilla.

In summary, two studies[16,18] that provided the same amount of vitamin D (500 μg) showed a significant reduction in GI scores at follow-up assessment. Three studies prescribed Ca and vitamin D, and the dosage varied from 375 μg to 800 μg[19–21]. Thus, no comparison can be performed. Two of the studies investigated the alveolar bone area using radiographic evaluations[19,21].

Quality of reporting of studies

The percentage of items reported using CONSORT ranged from 49 %[21] to 73 %[17] (Table 2). There were five unreported items for all the studies namely; changes to trial outcomes, interim analyses and stopping guidelines, changes to methods after trial commencement, the reason of the trial ended, and presentation of absolute and relative effect sizes. Three of the trials did not mention the randomisation in their title[19–21]. There was only one trial reported on the following items: the type of randomisation[17], description on the similarity of interventions[19] and the availability of the full trial protocol[19].

Risk of bias

Four of the studies (67 %) had low risk of bias arising from randomisation process[18–21] and due to missing outcome data[16,17,20,21]. Five studies (83 %) had low risk of bias due to deviation from intended intervention and due to measurement of the outcome[16–18,20,21]. With regards to selection of the reported result, three of the studies had low risk of bias[16,17,21], two studies had some concern[18,19] and one had high risk of bias[20]. The low risk of bias for the domains in all studies ranged from 20 % to 100 %, A study by Wical *et al.* (1979) has the highest percentage of low risk of bias and Batshutski *et al.* (2011) had the lowest percentage of low risk of bias. Four out of the five domains in Batshutski study were in some concern category (Table 3).

Discussion

This systematic review revealed that there was still insufficient evidence to support a positive relationship between vitamin D and oral health. Although the systemic search has retrieved many studies with regards to vitamin D and oral health, most of the studies were cross-sectional or observational studies. Higher-quality studies are required to assess the optimal dosage of vitamin D in relation to oral health. The reviewed papers were varied in terms of intervention(s) (mode of administration, dosage, frequency of use, duration) and outcomes.

In general, the systematic review revealed that vitamin D supplements with different dosages, mode of administration, duration and in combinations with other interventions (most notably Ca) showed a significant improvement in the outcomes measures, namely, periodontal health parameters, serum level of vitamin D, reduced bone loss, bone gain and tooth loss. The lowest dosage was reported by a study of Wical & Brussee (1979) which showed a significant reduction in alveolar bone loss associated with the intake of Ca and 375 USP of vitamin D. However, parameters such as serum level and periodontal conditions were not assessed in the study. The finding was in agreement with a study by Bashutski *et al.* (2011) that showed a combination of Ca and vitamin D improved linear bone gain. Another study by Krall *et al.* (2001) reported that tooth retention could be improved with Ca and vitamin D supplements. In addition, a study by Bashutski *et al.* (2011) also showed that sufficient vitamin D level (> 20 ng ml) at baseline was essential to enhance the bone gaining effects, improved PD, clinical attachment loss and BOP. Meanwhile, those studies with the lowest intake of Vitamin D (i.e. 500 μg) showed significant improvement of GI scores. Thus, it indicated that 500 μg would be the recommended dosage to maintain gingival health, and a combination of Ca and vitamin D would help to maintain bone level. Studies also showed that an increased dosage of vitamin D significantly increased the serum level of vitamin D. The review also revealed that the higher the dosage of vitamin D, the earlier the effect can be seen in the serum level and anti-inflammatory effect[17,18].

The importance of sunlight exposure for the synthesis of vitamin D by the skin was well established. The benefit may override the harmful effects, provided there is no excessive exposure to the sunlight[22]. The use of high sunscreens protection with high UV may compromise the serum vitamin D level[23]. However, daily or recreational sunscreen was not shown to compromise serum vitamin D level. There was only one study in this review that considered a sun exposure for the interventions group[16]. However, the results of the study cannot be generalised due to small sample size and additional intake of the dietary components. Moreover, the effects were also based on the dietary elements which make it difficult to provide evidence on which elements has the most impact on the outcome's parameters.

Studies have shown that a high dosage of vitamin D supplements was essential to reach the optimal serum level. However, the recommended target levels for vitamin D in the serum varied. A review paper reported serum vitamin D target levels ranging from 25 to 50 nmol/l or 10–20 ng/ml (corresponding to 400–800 μg daily intake of vitamin D supplementation which was varied with age)[24]. A recent review search in PubMed recommended the serum vitamin D target level (25-hydroxyvitamin D [25(OH) D] to be more than 50 nmol/l or 20 ng/ml[25]. Meanwhile, a clinical practice guideline described a vitamin D deficiency when the serum level of vitamin D is below 20 ng/ml (50 nmol/l), and vitamin D insufficiency at 21–29 ng/ml (55 to 75 nmol/l)[26].

Despite the importance of vitamin D, many people are not able to attain the optimal serum level of vitamin D daily. A single centre analysis study that involved approximately 610 000 patients from 136 countries reported that more than three-quarters of the patients were in the stage of serum vitamin D deficiency due to insufficient level[27]. Among them, the patients who were from the United Arab Emirates, Saudi Arabia and other middle eastern countries were those who had vitamin D deficiency. Another study was conducted on approximately 1500 Saudis' patients reported that the prevalence of female patients with vitamin D deficiency was high[28]. Although these countries typically have year-round sunshine, the low serum level of vitamin D among the population is a major concern. This could be related to their culture, religious practice and lifestyle. In addition, the serum vitamin D level also varied among people living in four different seasons. Their serum vitamin D levels were at a lower level during the winter months[29]. Hence, the importance of vitamin D supplementations and the risk of low serum level of vitamin D should be made aware to the target population.

With regards to the quality of reporting, studies are of 'moderate quality'. There were no details on such items in all studies; changes to trial outcomes, interim analyses and stopping guidelines, changes to methods after trial

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Table 2. CONSORT checklist for clinical trial studies

Heading	Item no.	Recommendation	P1	P2	P3	P4	P5	P6	*n*	%
Title and abstract	1	(a) Identification as a randomised trial in the title	1	1	1	–	–	–	3	43
		(b) Structured summary of trial design, methods, results, and conclusions	1	1	1	1	1	–	5	83
Background and Objectives	2	(a) Scientific background and explanation of rationale	1–2	1–2	1–2	1–2	1	1	6	100
		(b) Specific objectives or hypotheses	2	2	2	2	1	1	6	100
Trial design	3	(a) Description of trial design (such as parallel, factorial including allocation ratio)	–	2	2	2	1	1	5	83
		(b) Important changes to methods after trial commencement (such as eligibility criteria), with reasons	–	–	–	–	–	–	0	
Participants	4	(a) Eligibility criteria for participants	2	2	2	2	1–2	1	6	100
		(b) Settings and locations where the data were collected	2	2	2	2	–	1	5	83
Interventions	5	(a) The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2–3	2–3	2	2	2	1	6	100
Outcomes	6	(a) Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3	3	3	2	2–3	1–2	6	100
		(b) Any changes to trial outcomes after the trial commenced, with reasons	–	–	–	–	–	–	0	
Sample size	7	(a) How sample size was determined	3	2	2	–	–	–	3	50
		(b) When applicable, explanation of any interim analyses and stopping guidelines	–	–	–	–	–	–	0	
Sequence generation	8	(a) Method used to generate the random allocation sequence	3	2	3	–	–	1	4	67
		(b) Type of randomisation; details of any restriction (such as blocking and block size)	–	2	–	–	–	–	1	17
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.	3	–	3	–	–	1	3	43
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3	–	–	2	–	–	2	33
Blinding	11	(a) If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	–	–	3	2	–	1	3	43
		(b) If relevant, description of the similarity of interventions	–	–	–	2	–	–	1	17
Statistical methods	12	(a) Statistical methods used to compare groups for primary and secondary outcomes	3	3	4	2	2	4	6	100
		(b) Methods for additional analyses, such as subgroup analyses and adjusted analyses	3	3	4	2	2	–	5	83
Participants flow	13	(a) For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5	6	–	3	3	–	4	67
		(b) For each group, losses and exclusions after randomisation, together with reasons	5	6	3	–	2	4	5	83
Recruitment	14	(a) Dates defining the periods of recruitment and follow-up	3	2	2	2	3	1–3	6	100
		(b) Why the trial ended or was stopped	–	–	–	–	–	–	0	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	–	3	–	3	3	5	4	67
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups.	4	3	–	3	4	4–5	5	83
Outcomes and estimation	17	(a) For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95 % CI)	6	4–5	6–7	3	3–4	–	5	83
		(b) For binary outcomes, presentation of both absolute and relative effect sizes is recommended	–	–	–	–	–	–	0	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	6	6	7	3	–	–	4	67
Harms	19	All important harms or unintended effects in each group	5–6	7	8	5	4	5–6	6	100
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7	7	8	5	4	–	5	83
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7	7	8	–	5	7	5	83
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7	5–7	8	5	5	7	6	100
Registration	23	Registration number and name of trial registry	2	2	–	5	–	–	3	43
Protocol	24	Where the full trial protocol can be accessed, if available	–	–	–	2	–	–	1	17
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7	7	–	5	1	–	4	67
Total study										
n			26	27	23	25	20	18		
%			70	73	62	68	54	49		

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Table 3. Risk of bias

Bias domain	P1	P2	P3	P4	P5	P6
Bias arising from the randomisation process	Some concern The allocation sequence was random using web-based randomiser and adequately concealed. Baseline imbalances suggest a problem with the randomisation process.	Some concern Allocation was adequately concealed. Baseline imbalances suggest a problem with the randomisation process.	Low risk The allocation sequence was random and adequately concealed.	Low risk The allocation sequence was random and adequately concealed.	Low risk The allocation sequence was random and adequately concealed with stratification according to sex, race, and decade of age.	Low risk The allocation sequence was random using computer-generated and adequately concealed.
Bias due to deviations from intended interventions	Low risk Participants and investigators were unaware of the assigned intervention.	Low risk Participants and investigators were unaware of the assigned intervention.	Low risk Participants and investigators were unaware of the assigned intervention.	Some concern Participants were unaware of the assigned intervention and the operators did not evaluate the participants on who they performed the surgery.	Low risk Participants and investigators were unaware of the assigned intervention.	Low risk Participants and investigators were unaware of the assigned intervention.
Bias due to missing outcome data	Low risk The results were not affected by the dropped out subject from the experimental group.	Low risk There were no dropped out subjects.	Some concern An unclear information on proportion of missing data from allocated group. 10 % dropped out rate.	Some concern An unclear information on the data of the subjects that missed follow-up appointments.	Low risk There was evidence that the result was not biased by missing outcome data	Low risk There were no dropped out subjects.
Bias in measurement of the outcome	Low risk The assessors were unaware of the intervention received by the subjects during the assessment of the outcomes.	Low risk The assessors were unaware of the intervention received by the subjects.	Low risk The assessors were unaware of the intervention received by the subjects.	Some concern The assessors were not allowed to assess the participants of whom they did the surgery.	Low risk The assessors were unaware of the intervention received by the subjects	Low risk The assessors were unaware of the intervention received by the subjects
Bias in selection of the reported result	Low risk The analyses were used in accordance with a planned analysis. Reported outcome data are unlikely to have been selected, on the basis of the results.	Low risk Reported outcome data are unlikely to have been selected on the basis of the results.	Some concerns Analysis intention is not available.	Some concern There is insufficient information available to exclude the possibility that reported outcome data were selected, on the basis of the results.	High Risk There is insufficient information available on the reported primary outcome.	Low risk Reported outcome data are unlikely to have been selected on the basis of the results.

commencement, the reason the trial ended and presentation of absolute and relative effect sizes. Thus, there might be no such process during the study, or it was not reported. Nevertheless, reporting the details based on the CONSORT guideline would help to improve and guide future studies. Regarding the risk of bias within individual studies, lack and unclear information were the main contributing factors.

This review has some limitations. It is acknowledged that publication bias might have occurred during the selection of the studies from the databases. The selection was limited to English published papers and those that were available online. No authors were contacted and no papers in other languages were evaluated. However, involving more than one reviewer and using a broad search strategy helps reduce publication bias. The cross-reference of the published studies may also enhance it. In addition, the reporting of this systematic review was based on the time frames mentioned. Further updating information in the future is highly recommended. The published studies were relatively heterogenic, in particular the sample size, the intervention and outcomes of the study. Thus, the specific effects of vitamin D on oral health are not clear.

In conclusion, there are few clinical trials that have evaluated the effectiveness of vitamin D supplements to oral health. Among existing studies, there is substantial heterogeneity with respect to vitamin D interventions (mode of administration, dosages and duration of administration) and oral health outcomes assessed, as well as Ca supplementation added to the intervention. There are several shortcomings in the quality (of reporting) of studies and their risk of bias. Nonetheless, qualitative synthesis indicates some evidence to support the provision of vitamin D supplements for periodontal health. Further, high-quality clinical trials related to vitamin D interventions are warranted to provide a quantitative synthesis of their effectiveness.

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