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The impact of vitamin D deficiency on caries, periodontitis, and oral cancer: A systematic review

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ABSTRACT

Background: The relationship between vitamin D deficiency with dental caries, periodontitis and oral cancer is controversial.
Objectives: This review aimed to systematically evaluate the published literature and summarise the available evidence about the impact of vitamin D deficiency (VDD) on the oral diseases mentioned above.
Methods: PubMed, Web of Science, Scopus and ScienceDirect databases were used. The search terms included were vitamin D, caries, periodontitis, and oral cancer. All papers published between January 2017 and November 2022 were included. The PRISMA process was used for the screening and selection studies.
Results: Initially, 3001 studies were identified. However, after evaluating 46 full-text articles that explored the link between VDD and caries, periodontitis, and oral cancer, only 32 studies met the inclusion criteria for this systematic review. Among these, 15 studies focused on caries, 16 on periodontitis, and only one on oral cancer. Regarding study quality and risk of bias, 25 out of the 32 studies were deemed to have low risk. A total of 12 studies on periodontitis showed the impact of VDD.
Conclusion: The review highlights that most evidence suggests an association between VDD and periodontitis. However, findings concerning the association between VDD and dental caries were controversial. Thus, further research is required to clarify the impacts of VDD on caries and oral cancer.

1. Introduction

The impact of Vitamin D (VD) on oral health emphasizes its potential significance, urging a thorough understanding of its overall effect. Vitamin D deficiency (VDD) arises from reduced intake, sun exposure, and increased catabolism, leading to health disorders, including oral problems (Uwitonze et al., 2018; Weydert, 2014). VDD correlates with oral diseases like caries, periodontitis, and oral cancer (Botelho et al., 2020), with gene regulation issues reducing vitamin D production by up to 90 %.

Studies have linked dental caries to an increased risk of VDD in both children and adults (Almoudi et al., 2019; Botelho et al., 2020; Kim et al., 2018). Periodontal disease, also shows connections to VDD, affecting gingival health (Machado et al., 2020). Additionally, oral cancer, particularly oral squamous cell carcinomas, has associations with VDD, influenced by factors such as smoking and insufficient fruit and vegetable intake (Patil, 2021; Xie and Shang, 2022).

Numerous studies reported VDD's role in caries, periodontitis, and cancer, but some findings contradict (Akinkugbe et al., 2019; Botelho et al., 2020; Carvalho Silva et al., 2021; Duman et al., 2022; Hujoel, 2013; Machado et al., 2020; Patil, 2021; Zhou et al., 2021). Therefore, this systematic review aims to summarise the evidence on VDD's impact on caries, periodontitis, and oral cancer.

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2. Materials and methods

2.1. Study design

This systematic review was conducted following the PICO model, generating five queries. After discussions among researchers, three queries were chosen as research questions. This review focuses on children and adults as the population group, examining participants with deficient serum 25(OH)D levels as the Intervention. The comparison involves participants with sufficient serum VD levels, while the outcomes assessed include periodontitis, caries, and oral cancer. The main query seeks to establish any potential associations between VDD

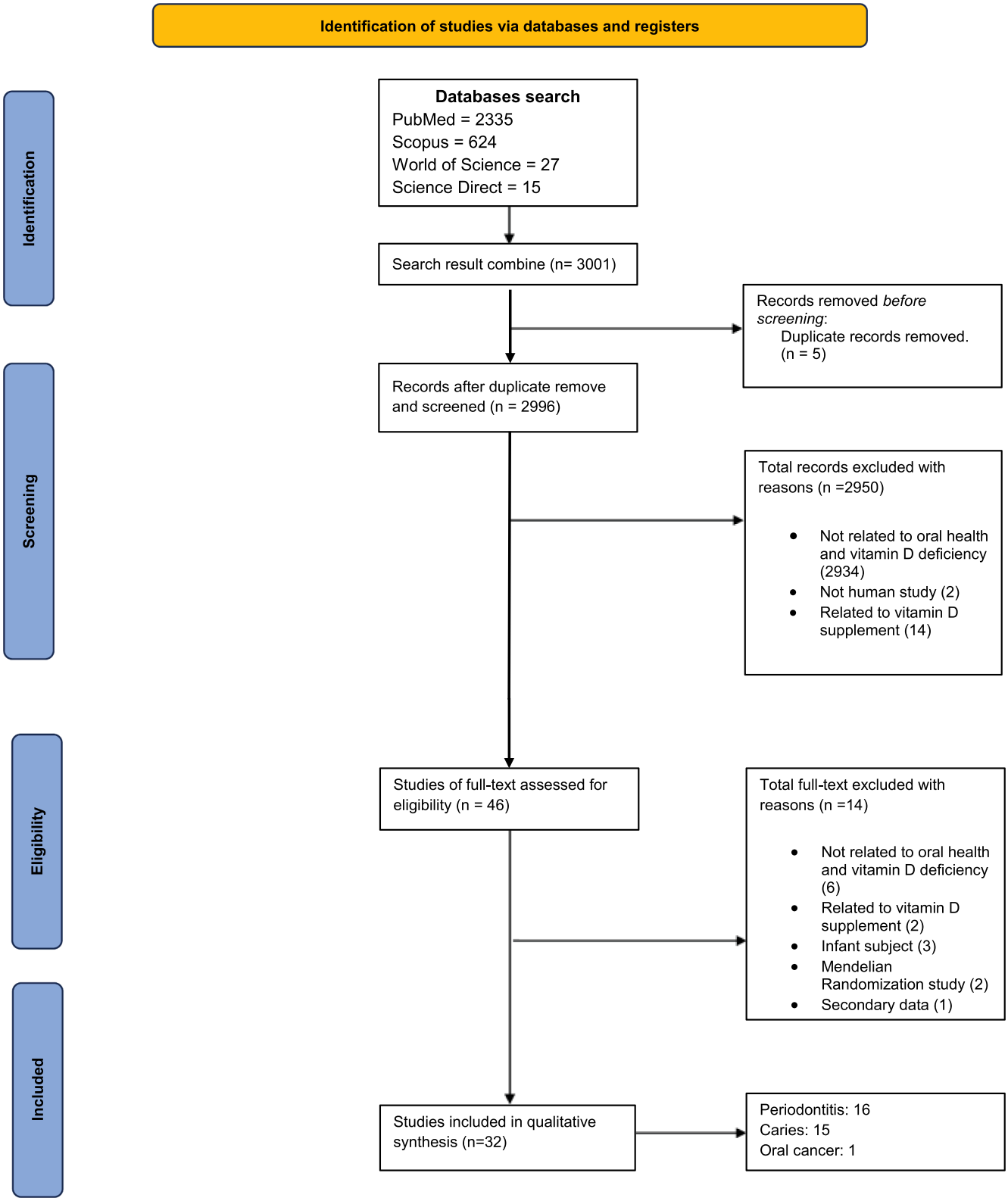

Fig. 1. PRISMA flow of the review process.

and periodontitis, caries, or oral cancer.

2.2. Search strategies

Two researchers systematically searched titles and abstracts of studies from 1st January 2017 to 16th November 2022, across four online databases: PubMed, Web of Science, Scopus, and ScienceDirect. This investigation encompassed both children and adults, focusing on interventions associated with VDD. Keywords utilised in the online databases included vitamin D, 25-hydroxyvitamin D, 25(OH)D, vitamin D deficiency, oral health, dental health, periodontitis, caries, and oral cancer. Additionally, reference lists were manually examined to identify pertinent articles meeting the inclusion criteria.

2.3. Study screening and selection

All studies were exported into Mendeley Reference Manager version 2.62.0 software after the screening of titles retrieved from the search to remove duplications. The full texts of the applicable articles were checked by the two reviewers individually. The abstract was read if there was any dispute about the title. Any discrepancies in the content were resolved through discussion and agreement by researchers. Relevant articles that related to the VDD and oral health were included for further screening. Papers that were found duplicated were removed. The articles were then divided according to periodontitis, caries, and oral cancer.

2.4. Eligibility criteria

The inclusion and exclusion criteria were established to refine the outcomes of the studies identified from the databases. Inclusion criteria for this study incorporated investigations exploring the correlation between VDD and periodontitis, caries, or oral cancer in the fields of science, medicine, and dentistry. It encompassed full-text articles in English, finalised for publication, and published from 1st January 2017 to 16th November 2022. Whereas, exclusion criteria involved the in vitro studies and review papers, as well as articles that did not meet the specified inclusion criteria.

2.5. Study selection and data collection process

Qualified studies underwent data extraction employing predetermined templates. Two researchers independently gathered and verified the data, consulting a third researcher for consensus. The flow of publications obtained from online databases was summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram (Fig. 1). The process commenced with a literature review, followed by screening of titles and abstracts, and a full-text assessment for eligibility. Discrepancies were resolved through discussion, leading to the exclusion of non-compliant articles. The final list of included studies was independently compiled into a standardised table using Google Sheet software, ensuring consistency through cross-checking. Extracted data included author names, publication years, age ranges, gene studies, Vitamin D Receptor (VDR) gene types, study designs, interventions, and VD correlations.

2.6. Study quality and risk of bias

The study's quality and bias were independently evaluated by two researchers using a modified systematic review template (Ismail et al., 2022). Criteria outlined in the articles, including population, sample size calculation, presence of study and control groups, study design, VD assessment, cut-off value, study findings, and limitations, were used to assess bias. A "/" was marked for reported criteria; otherwise, it was left blank. Based on the number of "/", articles were categorised: one to three as high bias, four to six as medium, and seven to nine as low.

3. Results

3.1. Study selection

A total of 3001 studies were initially identified through searches on PubMed, Scopus, Web of Science, and ScienceDirect. After eliminating duplicates (n = 5), two independent reviewers screened the remaining 2996 studies based on titles and abstracts. Among these, 2950 were excluded for not meeting inclusion criteria, such as being animal/laboratory-based, related to VD supplementation, or lacking VD interventions in oral health. Subsequently, the full texts of 46 potentially relevant studies were assessed, with 14 excluded for reasons such as focusing on Randomisation studies, infant/pregnant subjects, or lacking relevance to oral health and VDD. Finally, 32 studies met the inclusion criteria: 15 on caries, 16 on periodontitis, and one on oral cancer. The review process is illustrated in Fig. 1 (PRISMA flow diagram).

3.2. Study characteristics

Table 1, 2, and 3 detail the 32 studies (2017–2022) with varied designs, countries, and subjects' ages. There are 15 cross-sectional studies (Agrawal et al., 2019; Akinkugbe et al., 2019; Carvalho Silva et al., 2021; Dinda et al., 2020; Fatturi et al., 2020; Herzog and Ordóñez-Mena, 2022; Isola et al., 2020; Pratyusha et al., 2021; Seminario et al., 2018; Sufiawati et al., 2021; Wang et al., 2019; Yilidiz Telatar and Saydam, 2020; Yussif and Selim, 2021; Zhou et al., 2021, 2020), 10 case-control studies (Alzahrani et al., 2021; Aribam et al., 2020; Gupta et al., 2022; Ho et al., 2017; Jha et al., 2021; Ketharanathan et al., 2019; Marian et al., 2019; Nireeksha et al., 2022; Protyusha and Sundharam, 2021; Yuce et al., 2017), one combining both (Hussein et al., 2021), one clinico-biochemical study (Bhargava et al., 2019), and 5 without mentioned design (Anbarcioglu et al., 2019; Bayirli et al., 2020; Duman et al., 2022; Isola et al., 2021; Madalena et al., 2020). Among them, 19 focused on adults, 10 on children, one on both adults and children, and one did not specify age (Dinda et al., 2020). The studies investigated VDD's relationship with caries, periodontitis, and oral cancer, summarised in Tables 1, 2, and 3.

3.3. Risk of bias within studies

Table 4 outlines the bias risk assessment for the 32 analysed studies. None had high-risk bias, 5 exhibited medium risk, and 27 displayed low risk. Most studies omitted reporting on sample size calculation, cut-off value, and study design criteria.

3.4. Synthesis of results

Table 1, 2 and 3 summarise the main outcomes of the systematic review. Overall, most studies, 17 out of 32, indicated an association between VDD and caries, periodontitis, or oral cancer. Conversely, 10 studies reported no impact, and 5 studies had contradictory findings.

3.4.1. Caries

Studies categorised participants by decayed, missing, filled teeth (DMFT or dmft) scores to assess the association between VDR and caries risk (Table 1). Various genotyping techniques, including real-time real-time polymerase chain reaction (PCR) (Fatturi et al., 2020; Nireeksha et al., 2022; Yilidiz Telatar and Saydam, 2020), PCR-based restriction fragment length polymorphism (PCR-RFLP) (Aribam et al., 2020; Protyusha and Sundharam, 2021) or TaqMan chemistry and end-point analysis after DNA extraction (Madalena et al., 2020) were used for VDR polymorphism analysis. The most studied VDR genes were FokI (rs2228570) (Fatturi et al., 2020; Madalena et al., 2020; Nireeksha et al., 2022) and TaqI (rs731236) (Aribam et al., 2020; Protyusha and Sundharam, 2021; Yilidiz Telatar and Saydam, 2020), while the least studied were BgII (rs739837) (Fatturi et al., 2020; Madalena et al., 2020) and

Table 1
Caries studies details.

Author/Year	Country	Age group	Gene Study	VDR Gene Type	Study Design/ Subject	Intervention	Correlated To VD
Seminario et al., 2018	United States	Children	No	N/A	Cross-sectional study	- Serum VD obtained from the laboratory values section of the patient's health records through NHANES.Used dmft for caries recordBivariate and multivariable (modified) Poisson regression model used for data analysis	Yes
Akinkugbe et al., 2019	United States	Children	No	N/A	Cross-sectional study	- Serum VD obtained through NHANES VD data dmft score used for caries record	Conflicted
Aribam et al., 2020	India	Children	Yes	TaqI (rs731236)	Case-control study	- dmft score used for caries record Group divided according to DMFT score DNA extracted from salivaGenotype using PCR-RFLP	Yes
Madalena et al., 2020	Brazil	Children	Yes	FokI (rs2228570) and BgII (rs739837)	N/A	- DMFT score used for caries record Group divided according to caries experience DNA extracted from saliva Genotype using TaqMan chemistry	No
Fatturi et al., 2020	Brazil	Children	Yes	FokI (rs2228570) and BgII (rs739837)	Cross-sectional study	- DMFT score used for caries record Group divided according to caries experience DNA extracted from salivaGenotype using real-time PCR	No
Telatar et al., 2020	Turkey	Adult	Yes	TaqI (rs731236) and TFIP11 (rs5997096)	Cross-sectional study	- DMFT score used for caries record Group divided according to caries experience DNA extracted from buccal swabGenotype using real-time PCR	No
Zhou et al., 2020	United States	Adult	No	N/A	Cross-sectional study	- Serum VD obtained through blood samples DMFT score used or caries record Serums analysed using DiaSorin radioimmunoassayUnivariate multivariable-adjusted and sub-group for data analysis	Yes
Silva et al., 2021	Portugal	Children	No	N/A	Cross-sectional study	- Serum VD obtained through blood samples DMFT score used for caries record Serums analysed using competitive electrochemicalluminescence immunoassay protein-binding assayBivariate analysis and multivariate logisted regression used for data analysis	Yes
Jha et al.,2021	India	Children	No	N/A	Case-control study	- Serum VD obtained through blood samples Group divided into severe caries and no cariesDescriptive and bivariate statistics and logistic regression analysis for data analysis	Yes
Hussein et al., 2021	Malaysia	Children	No	N/A	Case-control, cross-sectional study	- Serum VD obtained through blood and saliva samples dmft score used for caries record Serums analysed using Enzyme-Linked Immunosorbent Assay KitDescriptive statistics, bivariate analysis, and Spearman's rank correlation for data analysis	No
Pratyusha et al., 2021	India	Children	No	N/A	Cross-sectional study	- Serum VD obtained through blood samples DMFT score used for caries record Serums analysed automated chemiluminescent immunoassay Independent sample *t*-test, linear regression analysis, and Pearson correlation test for data analysis	Yes
Protyusha et al., 2021	India	Adult	Yes	TaqI (rs731236)	Case-control study	- Measure dental caries using DMFT score DMFT score used for caries record Group divided according to caries experience DNA extracted from saliva Genotype using PCR-RFLP	Conflicted
Duman et al., 2022	Turkey	Children	No	N/A	N/A	- Serum VD obtained through blood samples DMFT score used for caries record Serums analysed by mass spectrometry on a LC/MS/MS system	Conflicted
Herzog et al., 2022	United States	Children	No	N/A	Cross-sectional study	- Serum VD obtained through NHANES VD data DMFT score used for caries recordMultivariable logistic and linear regression model used for data analysis	No
Nireeksha et al., 2022	India	Adult	Yes	FokI (rs2228570)	Case-control study	- DMFT score used for caries record Group divided according to caries experience DNA extracted from salivaGenotype using real-time PCR	Yes

N/A: Not applicable.

TFIP11 (rs5997096) (Yilidiz Telatar and Saydam, 2020).

Studies assessed VD serum levels using various methods, including electrochemical immunoassays, radioimmunoassays, ELISA kits, chemiluminescent immunoassays, and mass spectrometry (Carvalho Silva et al., 2021; Duman et al., 2022; Hussein et al., 2021; Pratyusha et al., 2021; Zhou et al., 2020). Some studies utilised data from the National Health and Nutrition Examination Survey (NHANES) (Akinkugbe et al., 2019; Herzog and Ordóñez-Mena, 2022; Seminario et al., 2018). Findings suggested an association between low VD serum levels and advanced caries in permanent teeth, while other studies reported inconsistent associations between VD status and caries experience (Akinkugbe et al., 2019; Carvalho Silva et al., 2021; Duman et al., 2022; Hussein et al., 2021; Jha et al., 2021; Pratyusha et al., 2021; Zhou et al., 2020). Generally,6 studies found no correlation between VDD serums or VDR gene and caries (Fatturi et al., 2020; Hussein et al., 2021; Madalena et al., 2020; Pratyusha et al., 2021; Yilidiz Telatar and Saydam, 2020), six revealed low VD serum levels or VDR gene linked with caries (Aribam et al., 2020; Carvalho Silva et al., 2021; Jha et al., 2021; Nireeksha

Table 2
Periodontitis studies details.

Author/Year	Country	Age Group	Gene Study	VDR Gene Type	Study Design/ Subject	Intervention	Correlated To VD
Ho et al., 2017	Taiwan	Adult	Yes	TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), FokI (rs2228570)	Case control study	- Used probing pocket depth (PPD) and clinical attachment loss (CAL) for periodontal assessment. DNA extraction obtained from blood serum. PCR-RFLP were used to genotype the VDR ANOVA test used for data analysis	Yes
Yuce et al., 2017	Turkey	Adult	No	N/A	Controlled clinical trial	- Used plaque index, gingival index, and CAL for periodontal assessment. Clinical periodontal measurements, gingival crevicular fluid (GCF) and blood samples was analysed. ELISA was used to measure GCF and serum VD TNF-, RANKL, and OPG. Chemiluminescence was used to measure serum VD levels in GCF and serum samples. one-way ANOVA was used for data analysis	Yes
Anbarcioglu et al., 2018	Turkey	Adult	No	N/A	N/A	- Used evaluated using PPD, CAL, inter-proximal attachment loss and radiographic evidence of alveolar bone loss for periodontal assessment. Serum VD level was obtained from the blood samples and measured using liquid chromatography mass spectrometry. Pearson $\chi 2$ test, ANOVA test and Tukey's test were used for data analysis	Yes
Agrawal et al., 2019	India	Adult	No	N/A	Cross sectional study	- Used PI, GI, PPD and CAL for periodontal assessment. Serum VD level was obtained from the blood samples and analysed using ELISA. Student's unpaired *t*-test and regression analysis were used for data analysis	Yes
Bhargava et al., 2019	India	Adult	No	N/A	Clinico-biochemical relationship study	- Used PI, GI, PPD and CAL for periodontal assessment Serum VD was analysed using ELISA. The data was statistically analysed using the SPSS software. Chi-square test, variance, and paired "t"-test were used for data analysis	Yes
Ketharanathan et al., 2019	Norway	Adult	No	N/A	Case control study	- Used CAL and PPD for periodontal assessment. Serum VD was obtained through blood sample and analysed using liquid chromatography. Radiographs were used to diagnose a marginal bone level. Mann-Whitney *U* test and Chi-square ($\chi 2$) test were used for data analysis.	Yes
Marian et al., 2019	Romania	Adult	Yes	BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236) and FokI (rs2228570)	Case control study	- Periodontal assessment was done by evaluating the PI, bleeding on probing, PPD, CAL and the number of lost teeth. DNA samples were extracted from the buffy coat. VDR polymorphisms were genotyped using real-time polymerase chain reaction Mann-Whitney test, Chi-squared tests and logistic regression models were used for data analysis.	Yes
Wang et al., 2019	China	Adult	No	N/A	Cross sectional study	- Measurements of PD and CAL were used to assess the condition of periodontium. Enzyme-linked immunosorbent assays were used to assess the serum concentrations of human VD in the blood samples. VDR expression in gingival tissue was assessed using immunohistochemistry. Chi-square test, two sample *t* test, Wilcoxon signed rank and ANCOVA were used for data analysis	Yes
Bayirli et al., 2020	Turkey	Adult	No	N/A	N/A	- Periodontal examination was done by evaluating PI, GI, PPD, BOP and CAL. The levels of 25(OH)D3 in the blood (ng/mL) were measured using liquid chromatography mass spectrometry. Gingival tissue samples were collected from the same individuals as GCFs samples prior to any periodontal therapy. ELISA method was used to determine the concentration of hBD-2 and LL-37 in gingival tissues and GCF. ANOVA, Tukey's HSD, Tamhane's T2 test,	Yes

(*continued on next page*)

Table 2 (*continued*)

Author/Year	Country	Age Group	Gene Study	VDR Gene Type	Study Design/ Subject	Intervention	Correlated To VD
						Kruskal Wallis test, Mann-Whitney U and Generalised additive model analyses were used for data analysis	
Dinda et al., 2020	Indonesia	N/A	Yes	VDR-1056 T/C	Cross sectional study	- The DNA was isolated from the blood serum. The polymorphism of the VDR-1056 T/C gene was investigated using the polymerase chain reaction-restriction (PCR) fragment length polymorphism method with Taq I restriction enzyme digestion. The Hardy Weinberg test and Fisher's exact test were used for data analysis	No
Isola et al.,2020	Italy	Adult	No	N/A	Cross sectional study	- Periodontal examination was done by evaluating PPD, CAL, BOP and PI. A commercial ELISA kit was used to assess the levels of 25(OH)D3 − 25(OH) D. Kruskal-Wallis test, Mann-Whitney test and Chi-squared test ($\chi 2$) were used for data analysis.	Conflicted
Alzahrani et al., 2021	Saudi Arabia	Adult	No	N/A	Case control study	- Used CAL and PPD for periodontal assessment. The serum concentrations of VD in blood samples were measured using an automated enzyme linked immunosorbent assay analyser. The student's *t*-test, Chi-square test, p-value and a multivariate logistic regression model were used for data analysis.	Yes
Isola et al.,2021	Italy	Adult	No	N/A	N/A	- The American College of Rheumatology categorization criteria were used to classify limited and diffuse SSc disease subtypes. Periodontal examination was done by evaluating BOP, CAL and PPD. The serum concentrations of VD in blood samples were measured using an automated enzyme linked immunosorbent assay analyser. The Kruskal-Wallis test, Mann-Whitney test, non-parametric Spearman test, Jonckheere-Terpstra test, various covariates, univariable and multivariable linear regression models were used for data analysis	Yes
Yussif et al, 2021	Egypt	Children & Adult	No	N/A	Cross sectional study	- The levels of VD3 in the blood (ng/mL) were measured using liquid chromatography-mass spectrometry. Periodontal examination was done by evaluating BOP, CAL and PPD. The Pearson correlation test, *t*-test, Anderson-Darling.	No
Zhou et al., 2021	United States	Adult	No	N/A	Cross sectional study	- A total oral periodontal examination programme was used for the periodontal examination, and probe measurements were taken at six sites per tooth in NHANES. Serum VD levels were measured in blood samples. DiaSorin radioimmunoassay kit was used for measuring serum VD. Univariate, multivariate, subgroup analyses, ANOVA, non-parametric test, Chi-square test, multivariate logistic regression model were used for data analysis.	No
Gupta et al.,2022	India	Adult	No	N/A	Case control study	- Used gingival index, mean ratio of BOP, oral hygiene index simplified, PPD, and CAL for periodontal assessment. Venous blood samples from the subjects were collected for the biochemical examination. A fully automated chemiluminescent immunoassay was used to calculate serum VD in ng/ml. A totally automated bidirectional analyser was used to measure red cell indices such as Hb, HCT, MCV, MCH, and MCHC. The Fisher's exact test, Student's *t*-test, Mann-Whitney *U* test and Pearson's correlation were used for data analysis.	Yes

N/A: Not applicable.

Table 3
Oral Cancer study details.

Author/Year	Country	Age Range	Gene Study	VDR Gene Type	Study Design/ Subject	Intervention	Correlated To VD
Sufiawati et al., 2021	Indonesia	Adult	No	N/A	Cross-sectional study	- Oral cancer clinically diagnosed and confirmed by histopathological examination. Serum VD obtained through blood samplesSerum VD measured using Human 25(OH) D ELISA Kit. Chi-square test and spearman rank test was used for data analysis	Yes

N/A: Not applicable.

Table 4
Assessment of Quality for Included Studies and Risk of Bias.

Study	Population	Sample size calculation	Study group (Vitamin D deficiency)	Control group (Normal serum vitamin D level)	Study design	Vitamin D assessment	Cutoff value/ vitamin D deficiency	The finding of the study (outcome)	The study limitation	Risk of bias* (Low/ Medium/ High)
Silva et al., 2021	/	X	/	X	X	/	/	/	/	Medium
Madalena et al., 2020	/	X	/	/	X	/	X	/	/	Medium
Telatar et al., 2020	/	X	/	/	/	/	X	/	/	Low
Zhou et al., 2020	/	X	/	/	/	/	/	/	/	Low
Fatturi et al., 2020	/	/	/	/	/	/	X	/	/	Low
Jha et al.,2021	X	X	/	/	/	/	/	/	/	Low
Protyusha et al., 2021	/	X	/	/	/	/	X	/	/	Low
Nireeksha et al., 2022	/	/	/	/	/	/	/	/	/	Low
Hussein et al., 2021	/	X	/	/	/	/	/	/	/	Low
Pratyusha et al., 2021	/	/	/	/	/	/	X	/	X	Low
Seminario et al., 2018	/	X	/	X	/	/	/	/	/	Low
Aribam et al., 2020	/	X	/	/	/	X	X	/	/	Medium
Duman et al., 2022	/	/	/	/	X	/	/	/	/	Low
Herzog et al., 2022	/	X	/	X	/	/	/	/	/	Low
Akinkugbe et al., 2019	/	X	/	/	/	/	/	/	/	Low
Zhou et al., 2021	/	X	/	/	/	/	/	/	/	Low
Bhargava et al., 2019	/	X	/	/	/	/	X	/	X	Medium
Bayirli et al., 2020	/	/	/	/	X	/	/	/	/	Low
Alzahrani et al., 2021	/	X	/	/	/	/	/	/	/	Low
Isola et al.,2020	/	/	/	/	/	/	/	/	/	Low
Gupta et al.,2022	/	/	/	/	/	/	/	/	/	Low
Wang et al., 2019	/	X	/	/	/	/	/	/	/	Low
Agrawal et al., 2019	/	/	/	/	/	/	X	/	/	Low
Isola et al.,2021	/	/	/	/	X	/	/	/	/	Low
Anbarcioglu et al., 2018	/	/	/	/	X	/	/	/	/	Low
Ketharanathan et al., 2019.	/	/	/	/	/	/	/	/	X	Low
Yuce et al., 2017	/	/	/	/	/	/	X	/	X	Low
Ho et al.,	/	/	/	/	/	/	X	/	X	Low
Yussif et al, 2021	/	/	/	/	/	/	/	/	/	Low
Marian et al., 2019	/	X	/	/	/	/	/	/	/	Low
Dinda et al., 2020	X	X	/	/	/	/	X	/	/	Medium
Sufiawati et al., 2021	/	X	/	/	/	/	/	/	X	Low

*one to three is ranked as high, four to six as medium and seven to nine as low.
/ = Yes, X = No.

et al., 2022; Seminario et al., 2018; Zhou et al., 2020) while three showed contradictory findings (Akinkugbe et al., 2019; Duman et al., 2022; Protyusha and Sundharam, 2021).

3.4.2. Periodontitis

After exploring the relationship between VDR and periodontitis, participants were categorised into periodontitis patients and healthy control groups. After evaluating periodontal conditions, DNA samples from human blood serum (Dinda et al., 2020; Ho et al., 2017) or buffy coat (Marian et al., 2019) were used for VDR genotyping via PCR-RFLP method (Dinda et al., 2020; Ho et al., 2017) or real-time PCR (Marian et al., 2019). Two studies focused on TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), and FokI (rs2228570) genotypes (Ho et al., 2017; Marian et al., 2019), while another discussed VDR-1056 T/C gene polymorphism (Dinda et al., 2020). Two studies found a correlation between VDR and periodontitis (Ho et al., 2017; Marian et al., 2019), but only one reported the opposite (Dinda et al., 2020).

Studies exploring the correlation between VD serum levels and periodontitis used the AAP Classification of Periodontal Diseases 1999 (Agrawal et al., 2019; Alzahrani et al., 2021; Bayirli et al., 2020; Bhargava et al., 2019; Isola et al., 2020; Wang et al., 2019; Yuce et al., 2017; Yussif and Selim, 2021; Zhou et al., 2021) and 2017 Classification of Periodontal and Peri-implant Diseases and Conditions (Gupta et al., 2022) for diagnosis. VD serum levels were analysed using different methods such as DiaSorin radioimmunoassay kit (Zhou et al., 2021), Enzyme-Linked Immunosorbent assay kit (Alzahrani et al., 2021; Bhargava et al., 2019; Isola et al., 2021, 2020; Wang et al., 2019; Zhou et al., 2021), liquid chromatography-mass (Anbarcioglu et al., 2019; Bayirli et al., 2020; Yussif and Selim, 2021), fully automated chemiluminescent immunoassay (Gupta et al., 2022), atmospheric pressure chemical ionisation-mass spectrometry in high-pressure liquid chromatography (Ketharanathan et al., 2019) or chemiluminescence (Yuce et al., 2017). Most studies revealed a relationship between VD levels and periodontitis, except for two studies (Yussif and Selim, 2021; Zhou et al., 2021). Additionally, one article reaching an inconclusive result (Isola et al., 2020).

In summary (Table 2), 12 articles supported a correlation between VD and periodontitis (Agrawal et al., 2019; Alzahrani et al., 2021; Anbarcioglu et al., 2019; Bayirli et al., 2020; Bhargava et al., 2019; Gupta et al., 2022; Ho et al., 2017; Isola et al., 2021; Ketharanathan et al., 2019; Marian et al., 2019; Wang et al., 2019; Yuce et al., 2017), while three articles denied this relationship (Dinda et al., 2020; Yussif and Selim, 2021; Zhou et al., 2021), and one article remined inconclusive (Isola et al., 2020).

3.4.3. Oral cancer

From Table 3, only one cross-sectional study assessed the relationship between serum VD 25(OH)D levels and oral cancer stage (Sufiawati et al., 2021). The study included 60 participants, 30 oral cancer patients (66.7 % women, 33.3 % men), and 30 healthy controls (66.7 % women, 33.3 % men). Serum 25(OH)D levels were measured using a Human 25 (OH)D ELISA Kit. The study revealed VDD in 61.5 % of oral cancer patients, with significantly lower VD serum compared to the healthy control group. Conclusively, the paper found no significant relationship between VD levels and oral cancer stages, although most oral cancer patients had VDD.

4. Discussion

In this systematic review, 32 articles were selected from 3001 screened journal articles, focusing on the qualitative impact of VDD on caries, periodontitis, and oral cancer. Most of the evidence supports the association between VDD and periodontitis, while the relationship with caries is inconclusive, with contradictory results across reviewed studies. Limited evidence is available for the impact on oral cancer, as only one paper was reviewed.

4.1. Caries

VD stimulates enamel mineralization through VDRs expressed in dental cells. VDD or VDR gene mutations can disrupt the VD pathway, reducing endogenous VD production by up to 90 %. Contradictory findings were observed in studies on VDR gene polymorphisms (Aribam et al., 2020; Fatturi et al., 2020; Madalena et al., 2020; Yilidiz Telatar and Saydam, 2020). Serum VDD showed a higher prevalence of dental caries, but the association with VDR gene receptors remains inconclusive.

Our examination of VDR gene polymorphisms, focusing on Fok1 and Taq1 genes, reveals potential associations with dental caries (Aribam et al., 2020; Fatturi et al., 2020; Madalena et al., 2020; Nireeksha et al., 2022; Yilidiz Telatar and Saydam, 2020). In studies on the *Fok1 Gene*, Fatturi et al. (2020) and Maladena et al. (2021) showed no direct correlation with caries incidence. Maladena et al. (2021) suggested an indirect impact on enamel formation, while Nireeksha et al. (2022) identified a clear link between Fok1 and active caries in specific VDR genotypes. For the *Taq1 Gene*, Telatar et al. (2020) found no significant association with high caries experiences in Turkish adults, while Aribam et al. (2020) proposed a potential predisposition to dental caries in individuals with specific Taq1 genotypes. Despite these valuable insights, a comprehensive understanding of the intricate relationships between VDR gene polymorphisms and dental caries remains elusive, necessitating further investigations (Aribam et al., 2020; Fatturi et al., 2020; Madalena et al., 2020; Nireeksha et al., 2022; Yilidiz Telatar and Saydam, 2020).

This review supports the association between VDD serum levels and dental caries, with studies reporting notable connections (Akinkugbe et al., 2019; Carvalho Silva et al., 2021; Duman et al., 2022; Herzog and Ordóñez-Mena, 2022; Hussein et al., 2021; Jha et al., 2021; Pratyusha et al., 2021; Seminario et al., 2018; Zhou et al., 2020). Silva et al. (2021) linked VD levels below 30 ng/mL in children to advanced dental caries, advocating optimal childhood VD for prevention. Zhou et al. (2020) associated deficient and insufficient VD levels in US adults with an increased dental caries incidence. Jha et al. (2021) identified malnourished children with severe caries exhibiting deficient VD. Pratyusha et al. (2021) recognised VD deficiency as a potential risk for dental caries. Seminario et al. (2018) demonstrated a significant association between suboptimal VD in children with special health needs and increased susceptibility to early childhood caries. However, Herzog et al. (2022) suggested that VD status did not influence caries in children aged 12 to 18, citing inconsistent associations. The association between serum and saliva VD and dental caries in young children remained inconclusive in a study by Hussein et al. (2021). Duman et al. (2022) faced challenges in confirming the relationship between VD levels and severe early childhood caries, reporting weak negative correlations. Akinkugbe et al. (2019) concluded that the association of deficient VD with a higher prevalence of caries remains inconclusive.

In conclusion, this review affirms the higher prevalence of dental caries with deficient serum VD levels, while the association with VDR gene receptors remains inconclusive. Further investigations are needed to understand the complex relationship between VDD and dental caries (Akinkugbe et al., 2019; Carvalho Silva et al., 2021; Duman et al., 2022; Herzog and Ordóñez-Mena, 2022; Hussein et al., 2021; Jha et al., 2021; Pratyusha et al., 2021; Seminario et al., 2018; Zhou et al., 2020).

4.2. Periodontitis

Previous studies highlight VD's role in the immune system, regulating immune cell function, with VDD linked to an increased risk of infection and autoimmune disorders (Dinda et al., 2020; Ho et al., 2017; Marian et al., 2019). VD influences the immune system by affecting lymphocyte growth, encouraging monocyte development, and increasing cytokine release (Dinda et al., 2020; Ho et al., 2017). The VDR gene, involved in VD metabolism, may play a role in periodontal

disease and bone tissue health (Dinda et al., 2020; Marian et al., 2019).

Studies exploring the VDR and periodontitis relationship investigated *TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410), and FokI (rs2228570)* genotypes (Ho et al., 2017; Marian et al., 2019) as these genotypes ascertain the VDR expressions and its activity. Dinda et al. (2020) focused on VDR-1056 T/C gene polymorphism as it influences bone metabolism and immune function that may result in bone resorption in periodontitis. Ho et al. (2017) linked VDR gene polymorphisms to aggressive periodontitis (AgP) and chronic periodontitis (CP) in the Taiwanese population. The f-allele of FokI acted as a genetic barrier preventing AgP. In Western Romania, Marian et al. (2019) found a connection between VDR polymorphisms (FokI and Bsml) and CP susceptibility. Discrepancies in research findings may be attributed to race and ethnicity (Dinda et al., 2020).

Studies on VD serum in periodontitis patients revealed insights. Zhou et al. (2021) showed a negative association between serum 25(OH)D and severe periodontitis. Yussif et al. (2021) found no significant link between periodontitis risk and serum VD level, and no correlation was observed between periodontal condition and VD levels. In the Indian community, Bhargava et al. (2019) and Isola et al. (2020) associated serum 25(OH)D levels with periodontal parameters. Alzahrani et al. (2021) and Gupta et al. (2022) summarised a significant association between periodontitis and low VD levels. Bayirli et al. (2020) linked serum VDD to decreased expression of antimicrobial peptides in periodontitis patients.

In summary, various studies suggest an association between VDR gene polymorphisms, serum VD levels, and periodontitis severity, emphasizing the need for further research (Ketharanathan et al., 2019).

4.3. Oral cancer

Sufiawati et al. (2021) found that 66.67 % of oral cancer patients had serum 25(OH)D deficiency, significantly different from healthy individuals. Low VD levels were associated with increased tumour aggressiveness, though no correlation with oral cancer stages was observed. VD supplements may benefit those at risk, potentially preventing or improving prognosis. However, limited studies on oral cancer in our review hinder conclusive findings.

5. Strengths and limitations

The study's strengths lie in its contemporary paper selection and thorough bias assessment, aiming to minimise publication bias. However, limitations comprised English-only studies and online full-text availability. Additionally, insufficient evidence for oral cancer hindered drawing conclusive VDD relations.

6. Conclusion

The findings of this review revealed that most of the evidence showed an impact of VDD with periodontitis. However, the association of VDD with dental caries was contradictory in the findings, whereby most VD serum levels studies showed an association with dental caries while the VDR gene studies revealed the opposite. Additionally, it was impossible to conclude the relationship of VDD with oral cancer as not many studies were conducted. Thus, further research is required to clarify the impacts of VDD on caries and oral cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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