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The correlation between serum vitamin D status and the occurrence of diabetic foot ulcers: a comprehensive systematic review and meta-analysis

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The association between vitamin D concentrations and the occurrence of diabetic foot ulcers (DFUs) remains a topic of ongoing debate. In order to provide a comprehensive and updated review, we conducted this meta-analysis to further investigate the relationship between vitamin D concentrations and DFUs occurrence. The following databases, including Cochrane Library, EMBASE, Web of Science, PubMed, CBM, CNKI, WANFANG DATA and VIP Database, were systematically searched for studies published up to Dec. 20th, 2023. The combined estimation was calculated using both fixed-effects and random-effects models. The overall effect size was reported as a weighted mean difference (WMD) with a corresponding 95% confidence interval (95%CI). Data analysis was performed utilizing Review Manager 5.4 and Stata 14. The Protocol has been registered in PROSPERO CRD42024503468. This updated meta-analysis, incorporating thirty-six studies encompassing 11,298 individuals with or without DFUs, demonstrated a significant association between vitamin D deficiency/insufficiency and an elevated risk of DFUs occurrence (< 25 nmol/L, OR 3.28, $P < 0.00001$; < 50 nmol/L, OR 2.25, $P < 0.00001$; < 75 nmol/L, OR 1.67, $P = 0.0003$). Vitamin D concentrations were significantly lower in individuals with DFUs compared to those without DFUs ($P < 0.00001$). Subgroup analyses consistently demonstrated this trend among the older population (> 50 years, $P < 0.00001$), individuals with long duration of diabetes (> 10 years, $P < 0.00001$), and those with poor glycemic control (mean HbA1c 8%-9% and > 9%, $P < 0.00001$).

Keywords Diabetic foot ulcers, Diabetes, Vitamin D, Systematic review and meta-analysis

Current research indicates that the occurrence of diabetic foot ulcers (DFUs) isnot only associated with traditional factors, such as diabetes-related peripheral neuropathy (DPN), peripheral arterial disease (PAD), and/or foot deformity[1,2], but also with the circulating levels of micronutrients[3]. In recent years, there has been growing attention towards the role of vitamin D insufficiency and deficiency in DFUs[4]. The reasonable assumption that vitamin D status may influence the risk of DFUs occurrence is supported by emerging evidence suggesting potential involvement of vitamin D in DPN[5,6] and PAD[7,8], which are significant contributors to the development of DFUs[1,2]. Furthermore, pre-clinical studies also provide supporting evidence for a potential role of vitamin D in wound healing[9,10].

However, the findings from observational studies have yielded inconsistent results. Recently, two meta-analyses[11,12] have reported an inverse association between vitamin D status and DFUs. Nevertheless, these analyses may be subject to potential limitations and were underpowered. Firstly, the incorporation of Chinese-language studies has been constrained, resulting in a limited number of included studies and sample size. Secondly, considering the variability in disease states and objectives, such as osteoporosis, rickets and osteomalacia, vitamin D deficiency is defined as less than 25 nmol/L, 30 nmol/L or 50 nmol/L[13]. Given the

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inherent ambiguity surrounding the precise definition of vitamin D deficiency, it is imperative to conduct additional comprehensive investigations to elucidate the potential association between vitamin D deficiency/insufficiency and DFUs. Moreover, despite the presence of a high degree of heterogeneity among studies, sensitivity analysis and subgroup analysis were not conducted, potentially leading to the oversight of significant confounding factors. Additionally, neither of these two meta-analyses provided any information regarding the detection method for vitamin D.

Therefore, it is imperative to recommence this analysis with more rigorous and detailed protocol. Moreover, we assert that our research is more comprehensive and representative owing to the utilization of larger and updated data.

Methods

Protocol and registration

This study presents a systematic review incorporating a meta-analysis conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines[14] and registered in PROSPERO (CRD42024503468). The reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15].

Data sources and searches

A comprehensive search was conducted by an experienced researcher (XR) across multiple databases, including Cochrane Library (Cochrane), EMBASE, Web of Science (WOS), PubMed, Chinese BioMedical Literature Database (CBM), CNKI, WANFANG DATA and VIP Database from inception until December 20th, 2023. The search was not limited by language restrictions. Additionally, the WHO International Clinical Trials Registry Platform was consulted to identify ongoing or unpublished potentially eligible trials that met the potential eligibility criteria. In order to ensure a comprehensive search for relevant articles, we manually examined the reference lists of identified trials and systematic reviews. The detailed search strategy can be found in Supplementary Table 1.

Study selection

The eligible studies were independently screened by two authors (WT and DC). In the event of any discrepancies, a consensus was achieved through thoroughly discussion. If an agreement could not be reached, a third experienced researcher (XR) was consulted. In accordance with the PECO strategy, we applied the following inclusion criteria: (1) Participants: adults (age $\geq$ 18 years) diagnosed with diabetes, irrespective of the presence or absence of DFUs; (2) Exposure: serum vitamin D concentrations (nmol/L or ng/ml) and categorization into deficient, insufficient and normal levels among study participants; (3) Comparison: the prevalence rate for vitamin D deficiency/insufficiency or variations in its levels by considering the presence or absence of DFUs; (4) Outcome: the prevalence of vitamin D deficiency/insufficiency or difference in levels of vitamin D; (5) Cross-sectional, cohort, or case-control studies without language or publication status restrictions. Case reports, case series, review articles, qualitative studies, and animal studies were excluded. Additionally, studies with incomplete data, incompatible formats, or non-convertible data were also excluded. The study eligibility assessment was conducted by two authors (WT and DC), with conflicts resolved through discussion with a third author (XR).

Data extraction and quality assessment

We extracted the data using predefined tables. The following information was recorded for each study: first author, year of publication, country where the study was conducted, study design, source of vitamin D in the samples, method used to determine vitamin D levels, sample size, gender distribution, vitamin D levels, age, body mass index (BMI), and HbA1c in both case and control groups. Continuous variables are depicted as mean and standard deviation (SD), categorical variables are depicted as number and percentages. For continuous variables expressed as median and interquartile range (IQR), we converted the data according to the preset method[16–19], and employed estimated mean and standard deviation (SD) for the final quantitative synthesis. Study quality was assessed using the Newcastle–Ottawa quality assessment scale (NOS)[20].

Data synthesis and statistical analysis

Continuous variables were pooled using the inverse variance random-effects model and were presented as mean differences with 95% CIs. Dichotomous variables were pooled using the Mantel–Haenszel method and presented as odds ratios (ORs) with 95% CI. The heterogeneity among the included studies was assessed using I^2 statistics. According to the results of heterogeneity analysis, appropriate pooled methods were selected: a random-effects model was employed if $I^2 > 50\%$, while a fixed-effects model was adopted if $I^2 \leq 50\%$. We evaluated the presence of publication bias through visual inspection of funnel plots and both Egger's and Begg's linear regression test when more than ten studies were available. To examine potential sources of heterogeneity, several a priori determined subgroup analyses were performed according to age, duration of diabetes and Hemoglobin A1c (HbA1c). Additionally, we used meta-regressions to explore potential confounders that may affect vitamin D concentrations. All data analysis was performed using Review Manager 5.4 and Stata 14, with a significance level set at 0.05.

Results

Literature search results

According to the search strategy, a total of 950 citations were initially identified from the eight databases and other sources. After removing duplicate studies (n = 302), we screened 648 potentially eligible records. Subsequently, based on title and abstract screening, 592 studies were excluded. Finally, 36 eligible studies were included in the meta-analysis. The selection process is visually depicted in Fig. 1 using a PRISMA flow diagram.

Study characteristics and quality assessment

The summarized characteristics of the included trials are presented in Table 1. All studies conducted between 2009 and 2023 were of an observational nature. A total of 11,298 participants were enrolled, with 3,450 cases in the DFU group and 7,848 cases in the non-DFU group. Sample sizes ranged from 26 to 4,284 with two studies[4,21] surpassing a sample size of over 1,000 participants. Out of the 36 studies included in this meta-analysis, 31 were conducted in Asia (20 in China, 7 in India, 2 in Iran, 1 each in Indonesia and Jordan), while 4 were carried out across Europe (located respectively in Belarus, Bulgaria, Germany and Greece), and one study was conducted in North America (in the USA). Serum concentrations of 25-Hydroxyitamin D were measured across all thirty-six studies, and reported as either nmol/L or ng/ml (1 ng/mL = 2.5 nmol/L). In eighteen studies, vitamin D status of patients was categorized and prevalence rates were reported for each category. Seven different detection methods for the determination of vitamin D were recorded. The quality assessment of the included studies is presented in Supplementary Table 2.

Variations in vitamin D concentrations and their impact on DFUs

Given the lack of consensus regarding the definition of vitamin D deficiency or insufficiency, we classified vitamin D concentrations into three distinct thresholds based on available data from the included studies, namely vitamin D < 25 nmol/L as Grade A, vitamin D < 50 nmol/L as Grade B and vitamin D < 75 nmol/L as Grade C.

Seven studies yielded data on vitamin D concentrations below 25 nmol/L, with 253 (45.59%) individuals with DFUs and 122 (20.37%) individuals with both diabetes and non-DFUs having concentrations of vitamin D below this threshold. The findings demonstrate a significant association between vitamin D concentrations below 25 nmol/L and the risk of developing DFUs (OR 3.28, 95% CI [2.52, 4.27], $P < 0.00001$; $I^2 = 0\%$, P-heterogeneity = 0.43) (Fig. 2A). As depicted in Fig. 2B, a total of 1545 (77.10%) patients with DFUs and 4317

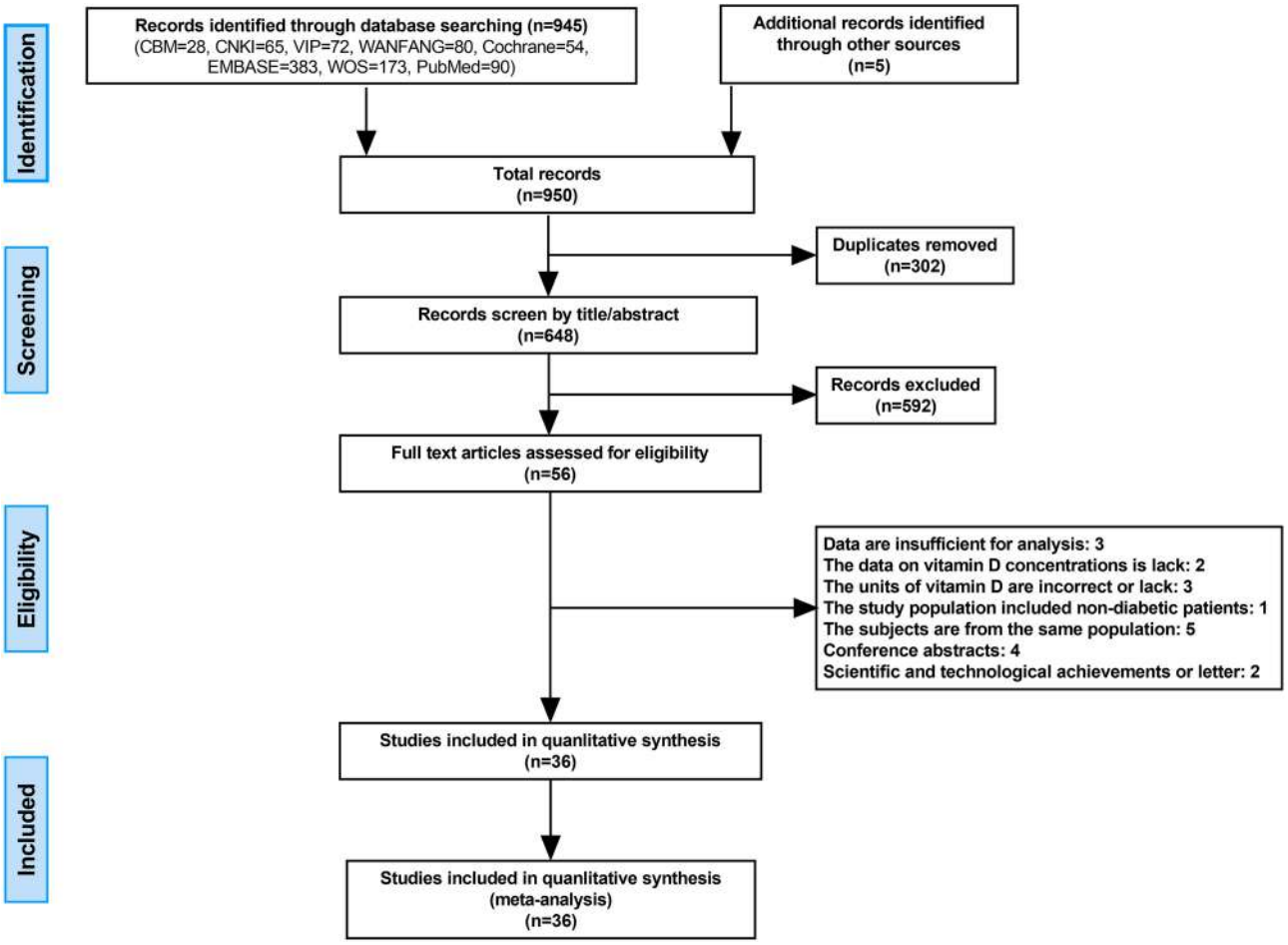

Fig. 1. Flow diagram illustrating the PRISMA protocol.

First author, year	Location	Study design	Language	Sample source (outpatient/inpatient)		Sample size (n)			Vitamin D assay	Mean vitamin D concentrations (nmol/L)		Male (%)	Mean age (years)	Mean BMI (kg/m^2)	Mean diabetes duration (years)	Mean HbA1c (%)
				DFU	Non-DFU	Total	DFU	Non-DFU		DFU	Non-DFU					
Afarideh et al. 2016[22]	Iran	Cross-sectional	English	Out	Out	60	30	30	ELISA	42	40	58.3	56.8	27.7	#N/A	8.2
Atoum et al. 2023[23]	Jordan	Cross-sectional	English	Out	Out	486	95	391	N	49.5	60.25	56.0	59.1	31.7	#N/A	8.5
Bao et al. 2019[24]	China	N	Chinese	N	N	110	50	60	ELISA	38.23	40.08	55.5	47.9	28.5	8.0	8.0
Chen et al. 2023[25]	China	N	English	N	N	160	80	80	CLIA	44	55.05	49.4	63.5	24.7	#N/A	#N/A
Dai et al. 2020[26]	China	N	English	In	In	51	21	30	RIA	28.03	44.33	56.9	60.4	24.8	10.4	8.5
Darlington et al. 2019[27]	India	Cross-sectional	English	Out	Out	176	88	88	ELISA	57.98	73.98	#N/A	57.3	24.4	#N/A	9.5
Deng et al. 2015[28]	China	N	Chinese	In	In	120	60	60	ECL	45.1	52.2	52.5	62.7	#N/A	13.0	8.9
Feldkamp et al. 2018[29]	Germany	N	English	Out/in	Out/in	207	104	103	RIA	29.5	47.5	#N/A	69.8	#N/A	17.2	#N/A
Gupta et al. 2016[30]	India	N	English	Out	Out	100	50	50	RIA	35.63	53.2	63.0	52.1	23.7	4.5	9.9
Hong et al. 2017[31]	China	N	Chinese	N	N	70	30	40	ELISA	38	40	#N/A	42.0	28.8	8.0	8.0
Ignatovich et al. 2014[32]	Belarus	N	Russian	N	N	40	22	18	N	24.62	43.87	45.0	#N/A	#N/A	#N/A	#N/A
Kota et al. 2013[33]	India	N	English	N	N	200	100	100	RIA	40.25	49.5	64.0	53.4	#N/A	#N/A	10.6
Li et al. 2021[34]	China	Case–Control	Chinese	In	In	47	26	21	CL	44.15	59.48	61.7	55.0	23.3	5.3	10.5
Li et al. 2023[35]	China	N	Chinese	N	N	120	60	60	CLIA	40	50.05	60.0	63.3	24.5	#N/A	#N/A
Lu et al. 2019[36]	China	Case–Control	Chinese	In	In	120	60	60	CL	45.63	61.28	#N/A	61.5	#N/A	10.4	8.9
Luo et al. 2019[37]	China	N	Chinese	Out	Out	80	40	40	ECL	24.45	35.78	58.8	55.0	24.6	4.7	8.2
Najafipour et al. 2019[38]	Iran	N	English	N	N	70	35	35	CLIA	42.15	59.75	62.9	59.2	28.4	12.0	8.4
Priyanto et al. 2023[39]	Indonesia	Cross-sectional	English	Outpatient	Outpatient	81	41	40	CLIA	21.91	40.71	39.5	56.0	26.6	7.4	8.1
Shen et al. 2015[40]	China	Cross-sectional	Chinese	Out/in	Out/in	53	21	32	RIA	41.75	73	52.8	57.3	30.3	7.1	8.9
Tang et al. 2022[4]	China	N	English	In	In	1721	547	1174	ECLIA	36.74	46.09	49.2	66.3	24.3	#N/A	8.0
Tang et al. 2023[41]	China	N	English	In	In	256	156	100	CLIA	29.17	40.83	55.5	55.3	#N/A	7.5	9.0
Tiwari et al. 2013[42]	India	N	English	N	N	289	125	164	RIA	40.25	50.75	65.1	52.1	24.4	6.1	9.6
Tiwari et al. 2014[43]	India	N	English	Out	Out	219	112	107	RIA	40.2	49.4	67.6	52.8	24.0	6.6	9.4

Continued

First author, year	Location	Study design	Language	Sample source (outpatient/inpatient)		Sample size (n)			Vitamin D assay	Mean vitamin D concentrations (nmol/L)		Male (%)	Mean age (years)	Mean BMI (kg/m^2)	Mean diabetes duration (years)	Mean HbA1c (%)
				DFU	Non-DFU	Total	DFU	Non-DFU		DFU	Non-DFU					
Tiwari et al. 2022[44]	India	N	English	In	In	173	100	73	RIA	40.25	49.4	#N/A	52.9	24.0	6.6	9.4
Todorova et al. 2022[45]	Bulgaria	Cross-sectional	English	N	N	136	73	63	ECLIA	29.71	39.22	63.2	58.1	30.9	#N/A	8.4
Tong et al. 2023[46]	China	N	Chinese	N	N	210	160	50	ELISA	24.8	37.73	55.7	60.0	#N/A	#N/A	8.7
Tsitsou et al. 2023[47]	Greece	Cross-sectional	English	Out	Out	68	33	35	LC–MS/MS	44.75	49.5	75.0	64.1	29.7	15.7	6.9
Wang et al. 2022a[48]	China	N	English	In	In	429	242	187	ECLIA	28.28	37.78	64.3	62.3	24.9	14.8	8.7
Wang et al. 2022b[49]	China	N	English	In	In	339	204	135	N	30.49	38.14	62.8	67.2	24.5	17.2	8.5
Wang et al. 2022c[50]	China	N	Chinese	N	N	160	80	80	CL	47.18	56.03	74.4	64.9	25.0	11.4	9.9
Wu et al. 2015[51]	China	N	Chinese	N	N	48	24	24	ELISA	25.8	31.7	58.3	55.5	#N/A	8.9	8.9
Xiao et al. 2020[21]	China	Cross-sectional	English	In	In	4284	245	4039	CL	36.96	40.97	52.6	#N/A	#N/A	#N/A	#N/A
Yoho et al. 2009[52]	USA	N	English	N	N	26	13	13	N	35.2	43.45	73.1	63.6	#N/A	#N/A	#N/A
Zhang et al. 2013[53]	China	N	Chinese	In	In	85	41	44	ELISA	26.56	32.23	70.6	56.5	24.5	12.6	8.9
Zhang et al. 2022[54]	China	N	Chinese	In	In	180	120	60	ECL	24.55	37.55	64.4	55.4	24.4	#N/A	8.6
Zubair et al. 2013[55]	India	Prospective cohort	English	In	In	324	162	162	RIA	20.56	74.68	63.3	46.7	24.4	#N/A	8.8

Table 1. Summary characteristics of included studies. *CL* chemiluminescence; *CLIA* chemiluminescent immunoassay; *ECL* electrochemiluminescence; *ECLIA* electrochemiluminescent immunoassay; *ELISA* enzyme-linked immunosorbent assay; *LC–MS/MS* liquid chromatography-tandem mass spectrometry; *RIA* radioimmunoassay; *N* not reported.

(65.56%) individuals without DFUs exhibited vitamin D concentrations below 50 nmol/L across thirteen studies, which was also associated with an elevated risk of DFUs (OR 2.25, 95% *CI* [1.80, 2.80], $P < 0.00001$; $I^2 = 55\%$, *P*-heterogeneity = 0.009) (Fig. 2B). The absence of publication bias was indicated by the funnel plot as well as the Egger and Begg tests (Egger $P = 0.252$, Begg $P = 0.246$) (Supplementary Fig. 2B). In relation to vitamin D concentrations below 75 nmol/L, a total of ten studies involving 253 (45.59%) patients in the DFUs group and

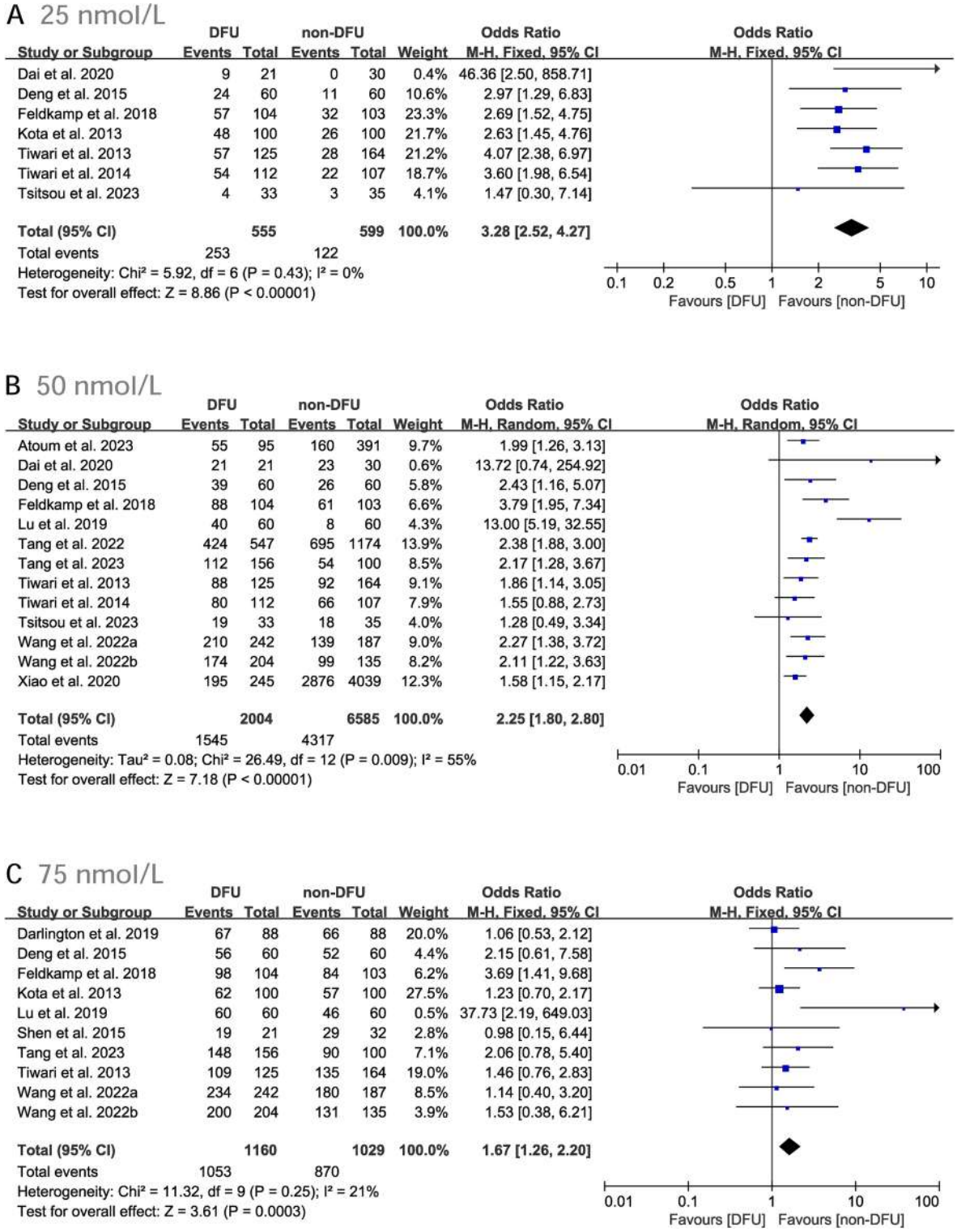

Fig. 2. **A, B, C** Forest plot illustrating the association between DFUs and varying thresholds of vitamin D levels. **A**: 25 nmol/L, **B**: 50 nmol/L, **C**: 75 nmol/L. df, degrees of freedom; IV, inverse variance; M-H, Mantel–Haenszel.

122 (20.37%) patients in the non-DFUs control group were identified. Notably, a statistically significant disparity persisted in the incidence of DFUs between these two groups (OR 1.67, 95% *CI* [1.26, 2.20], $P=0.0003$; $I^2=21\%$, *P*-heterogeneity = 0.25) (Fig. 2C). The analysis of bias tests using funnel plots, Egger and Begg tests did not reveal any significant publication bias (Egger $P=0.085$, Begg $P=0.283$) (Supplementary Fig. 2C).

Vitamin D concentrations and DFUs

As depicted in Fig. 3A, the meta-analysis employed a random-effects model to analyze all 36 studies. The findings demonstrated a significant reduction in serum vitamin D levels among patients with DFUs compared to individuals without DFUs (WMD = −10.80, 95% *CI* [−11.89, −9.71], $P<0.00001$). The heterogeneity tests indicated substantial heterogeneity among the included studies ($I^2=88\%$, *P*-heterogeneity < 0.00001). The absence of asymmetry observed in the funnel plot (Fig. 3B) analysis suggests no evidence of publication bias. Furthermore, both the Egger test ($P=0.44$) and Begg test ($P=0.205$) did not identify any significant small study effects.

The heterogeneity observed in this study was not attributed to any individual study, and a total of eight studies[21,24,25,31,35,39,40,55] with a high risk of bias were identified. However, excluding these eight studies that contributed the most to between-study heterogeneity did not significantly alter the results (WMD = −10.93, 95% *CI* [−12.20, −9.65], $P<0.00001$). Furthermore, this exclusion led to a substantial reduction in heterogeneity ($I^2=52\%$, *P*-heterogeneity = 0.0007) (Supplementary Fig. 3).

Subgroup analysis

Subgroup analysis was conducted to evaluate the potential interaction between vitamin D and other factors.

Initially, variations in the association between vitamin D and DFUs were observed across different age groups. Among studies with a mean age of 50 years or younger, there was no statistically significant difference in vitamin D concentrations between patients with DFUs and individuals without DFUs (WMD = −18.77, 95% *CI* [−38.77, 1.23], $P=0.07$; $I^2=99\%$, *P*-heterogeneity < 0.00001). However, in individuals aged over 50 years, the DFUs group exhibited significantly lower vitamin D concentrations compared to the non-DFUs group. Notably, heterogeneity decreased across studies without reaching statistical significance for interaction (WMD = −10.95, 95% *CI* [−11.77, −10.13], $P<0.00001$; $I^2=70\%$, *P*-heterogeneity < 0.00001; *P*-interaction = 0.44) (Supplementary Fig. 4).

The results demonstrated robustness and consistency across various subgroups based on the duration of diabetes, thereby highlighting their generalizability. Furthermore, a notable reduction in heterogeneity was observed specifically within the subgroup characterized by an average diabetes duration exceeding 10 years (WMD = −10.48, 95% *CI* [−13.31, − 7.64], $P<0.00001$; $I^2=60\%$, *P*-heterogeneity = 0.008) (Supplementary Fig. 5).

Considering the potential interaction between vitamin D concentrations and glycemic control, we further stratified mean HbA1c values into three subgroups (≤8%, 8–9% or > 9%). Upon comparing these three subgroups, no significant difference in vitamin D concentrations was observed in patients with or without DFUs when mean HbA1c was less than or equal to 8% (mean HbA1c ≤ 8%, WMD = −2.06, 95% *CI* [−4.18, 0.06], $P=0.06$; $I^2=0\%$, *P*-heterogeneity = 0.84). However, the vitamin D concentrations were significantly lower in the DFUs group compared to the non-DFUs group, when mean HbA1c values were ranging from 8 to 9% (mean HbA1c 8%-9%, WMD = −13.63, 95% *CI* [−16.51, − 10.76], $P<0.00001$; $I^2=89\%$, *P*-heterogeneity < 0.00001). In subgroup analysis involving individuals with mean HbA1c values greater than 9%, those with DFUs exhibited significantly lower vitamin D concentrations compared to those without DFUs, and heterogeneity between studies was reduced (mean HbA1c > 9%, WMD = −9.38, 95% *CI* [−10.37, − 8.39], $P<0.00001$; $I^2=0\%$, *P*-heterogeneity = 0.51). Furthermore, a significant interaction was observed among the three subgroups based on mean HbA1c values (*P*-interaction < 0.00001) (Supplementary Fig. 6).

Additionally, the meta-regression analysis investigating the influence of geographical location, gender, BMI and research quality on the risk of DFUs did not yield statistically significant results.

Discussion

This meta-analysis of thirty-six observational studies, encompassing patients with or without DFUs, revealed a significant correlation between vitamin D insufficiency and deficiency, and an elevated risk of developing DFUs. Furthermore, lower serum concentrations of vitamin D were found to be associated with an increased susceptibility to DFUs. Additionally, our meta-analysis found a significant association between low serum vitamin D levels and the presence of DFUs. This association was particularly pronounced in older patients with longer diabetes duration and poorer glycemic control.

Although several single-center randomized controlled trials (RCTs)[56–60] with a limited sample size have been conducted, the current evidence on this topic primarily relies on observational studies. Therefore, it is important to emphasize that our findings do not necessarily establish a direct causal relationship between vitamin D and DFUs. It is worth noting that there are two evident confounding factors that imped causal inference. Firstly, it is well-established that vitamin D synthesis primarily occurs in the skin following exposure to ultraviolet B radiation from sunlight[61]. Therefore, engaging in appropriate outdoor activities becomes crucial for maintaining normal serum vitamin D levels. The decline in outdoor activities among patients with DFUs and those at high risk cannot be overlooked, as it may contribute to the observed low serum vitamin D levels. Secondly, a significant inverse association has been reported between serum vitamin D and obesity[62], which is particularly relevant considering the majority of type 2 diabetic patients are overweight or obese. However, numerous significant potential mechanisms revealed by preclinical studies may hypothetically elucidate the augmented risk of DFUs in individuals with both diabetes and low vitamin D concentrations. Firstly, vitamin D plays a pivotal role in regulating the proliferation, migration, and differentiation of keratinocytes. In addition to

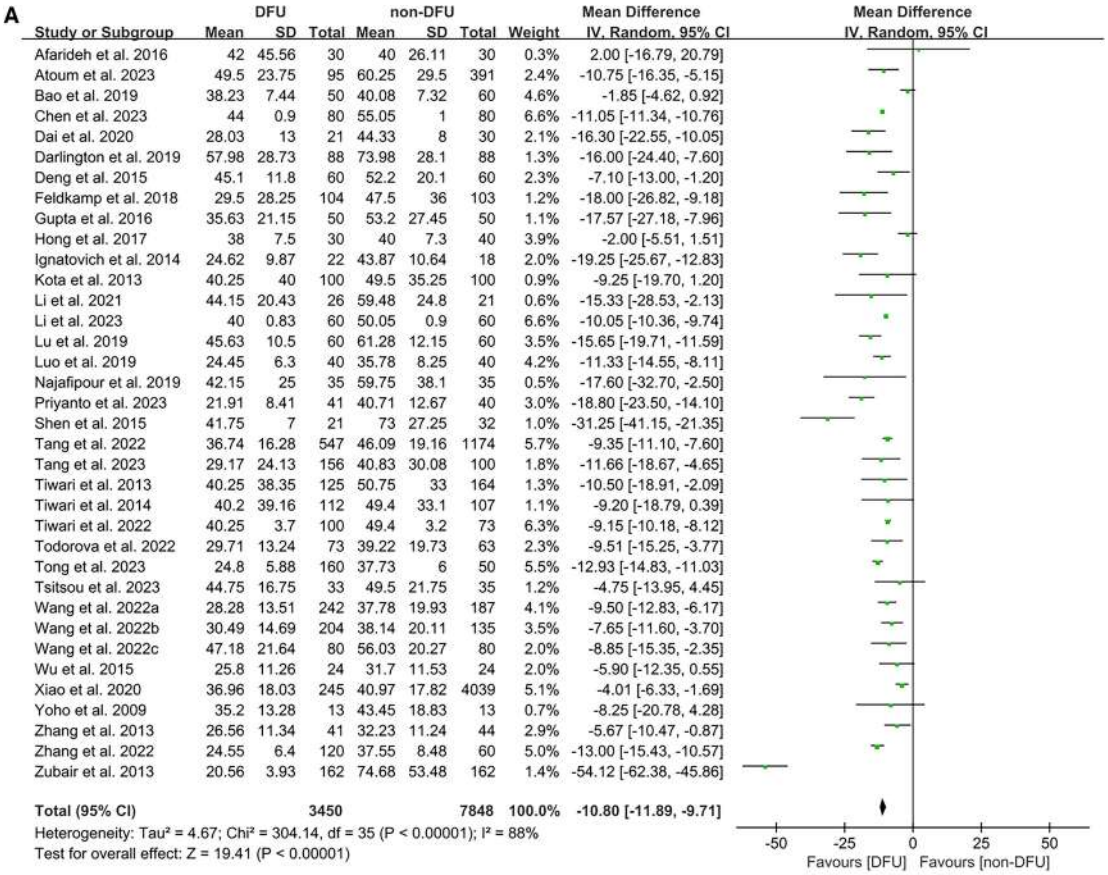

Fig. 3. **A** Forest plot illustrating the vitamin D concentrations in patients with DFUs or non-DFUs. **B** Funnel plot illustrating the vitamin D concentrations in patients with DFUs or non-DFUs.

serving as the primary source of vitamin D, the keratinocytes in the epidermis and hair follicle express all the necessary enzymes for vitamin D metabolism[63]. Conditional VDR knockout mice exhibit impaired self-renewal, activation, and migration of epidermal stem cells due to inhibition of β-catenin signaling, resulting in delayed re-epithelialization and wound closure[64]. Furthermore, topical application of vitamin D has been demonstrated to enhance wound healing[65]. Additionally, vitamin D plays a pivotal role in modulating immune and inflammatory responses. Supplementation with vitamin D can attenuate the expression of proinflammatory cytokines such as

IL-6, IL-1β, MCP-1 and TNFα by inhibiting AMPK activation and nuclear NF-κB phosphorylation[66]. On the contrary, the normal inflammatory response is facilitated through interaction with the TGF-β signaling pathway and enhancement of VDR-Smad3 complex formation[67]. Besides, vitamin D exerts its influence on the innate immune system by impacting antigen-presenting cells (APC) and inducing expression of antimicrobial peptides (AMPs)[68], while also regulating adaptive immunity by modulating the activities of T-helper cells, T-regulatory cells and B cells[69]. Thirdly, it can enhance angiogenesis by upregulating the expression of pro-angiogenic factors such as vascular endothelial growth factor A, hypoxia-inducible factor-1α and angiogenin[70]. Moreover, vitamin D deficiency may contribute to clinical diabetic small fibre neuropathy through its impact on nerve growth factor (NGF), which governs phenotype and sensitivity of nociceptor fibres[71], while chronic administrations of vitamin D has been shown to alleviate behavioral scores associated with neuropathic pain in rats[72]. These mechanisms substantiate the ongoing interest among clinical researchers in exploring the relationship between vitamin D and DFUs, thereby highlighting the increasing attention garnered by the clinical significance of vitamin D supplementation in DFUs. Therefore, despite the potential influence of various factors such as outdoor activities and obesity on serum vitamin D levels in patients with DFUs, pertinent data from preclinical investigations still substantiate the plausible causal roles of vitamin D in the pathophysiology of DFUs.

However, the current available observational studies on vitamin D and DFUs have yielded inconsistent findings. While the majority of studies indicated lower vitamin D concentrations in patients with DFUs compared to those without DFUs, a minority of others conducted in India[27], Greece[47] and China[31,73] reported no statistically significant difference. Interestingly, a cross-sectional study conducted in Iran[22] even yielded conflicting findings. Notably, in 2019, Jiezhi Dai et al.[74] performed the inaugural meta-analysis on this subject matter, encompassing seven studies involving 1,115 patients. Their analysis revealed a significant decrease in vitamin D levels among patients with DFUs (MD − 13.47 nmol/L, 95% *CI* [− 16.84, − 10.10], $P < 0.00001$; *P*-heterogeneity = 0.34, $I^2 = 12\%$) and established an association between severe vitamin D deficiency and an elevated risk of DFUs (OR 3.22, 95% *CI* [2.42 − 4.28], $P < 0.00001$; *P*-heterogeneity = 0.64, $I^2 = 0\%$). However, the limited number of included studies and inadequate sample size of researched objects constrain the strength of their evidence. In recent years, two similar meta-analyses have been reported[11,12]. However, regrettably, neither of them encompassed studies published in Chinese. Moreover, studies yielding non-significant results[27,31,73] were also excluded, potentially introducing bias. Additionally, the lack of standardization in the units used for vitamin D measurements in these two reviews may potentially impact the reliability of results. For instance, Xin Li et al.'s[11] meta-analysis published in 2023 reported vitamin D concentrations as ng/ml in six out of fifteen included studies[26,39,41,44,45,47], while others utilized nmol/L. Furthermore, in another meta-analysis conducted by Juan Lin et al.[12] during the same year, there were inaccuracies in evaluating sample sizes for two of twelve studies included[55,75]. Lastly, the high heterogeneity observed across studies highlighted by both reviews was not addressed through subgroup or meta-regression analysis. This oversight may have overlooked significant potential confounding factors.

There are two significant distinctions between previous reports and our study. Firstly, we conducted a comprehensive evaluation of all relevant studies published in Chinese, which were included in the current analysis. Additionally, we incorporated three recently published studies from Oct 2023 with an aggregate sample size exceeding 800 patients that were previously unavailable for inclusion. These additions facilitated the acquisition of more extensive data, thereby enhancing statistical power. Secondly, to investigate potential sources of heterogeneity, we performed sensitivity, subgroup analyses, and meta-regression analyses to augment the credibility and reliability of our findings. Furthermore, by implementing more detailed grading system for vitamin D concentrations, we aimed to explore any possible linear relationship between vitamin D levels and the risk of DFUs.

In addition to conventional comparison, given the substantial heterogeneity ($I^2 = 88\%$) observed in the overall forest plot and the multitude of influencing factors associated with vitamin D, we further conducted subgroup analyses based on age, duration of diabetes, and glycemic control.

An intriguing finding from the subgroup analysis based on age is that a significant disparity in vitamin D levels was observed only among individuals aged 50 years or older ($P < 0.00001$), whereas no such difference was found in patients younger than 50 years ($P = 0.07$). Furthermore, the heterogeneity ($I^2 = 70\%$) substantially decreased within the subgroup of older patients (> 50 years), although no statistically significant differences were observed between subgroups ($P > 0.05$). The decline in vitamin D concentrations with advancing age can be attributed to various factors, including variations in dietary intake, metabolic dysfunctions, and diminished vitamin D receptors[76,77]. Consequently, there is a significant degree of interindividual variation in vitamin D concentrations, which tends to increase with advancing age. Notably, perimenopausal and postmenopausal women exhibit a higher prevalence of lower serum levels of vitamin D[78], potentially contributing to inconsistent findings observed across different age subgroups.

In the subgroup analysis of varying durations of diabetes, patients with DFUs exhibited comparatively lower concentrations of vitamin D compared to those without DFUs in the subgroup with a disease duration exceeding 10 years, resulting in a significant reduction in heterogeneity among studies. These findings suggest that the duration of diabetes may contribute to the observed heterogeneity.

In the subgroup analysis of different glycemic control statuses, a statistically significant difference in vitamin D levels was only observed in the population with poor blood sugar control (mean HbA1c 8%-9% and > 9%, $P < 0.00001$), but not in those with acceptable glycemic control (mean HbA1c ≤ 8%, $P = 0.06$), accompanying with a significant differences between the subgroups (*P*-interaction < 0.00001). Actually, the impact of vitamin D on glycemic control continues to garner attention, as evidenced by a recent RCT demonstrating its preservation of vitamin D on pancreatic β-cell function[79]. Overall, Vitamin D supplementation has been shown to have a beneficial effect in reducing insulin resistance[80] and improving glycemic control[81]. This finding

partially elucidates why significant disparities in vitamin D levels were observed solely among individuals with suboptimal glycemic control.

Furthermore, we conducted a comprehensive meta-regression analysis accounting for potential confounding factors such as geographical location, gender, BMI and research quality that could potentially impact the outcomes of vitamin D studies. However, despite our diligent efforts, we did not find any significant associations. Unfortunately, owing to the unavailability of data, we were unable to account for several potentially significant confounding factors, including blood draw season, diabetes medication usage, physical activity levels and duration of outdoors exposure during summer. Additionally, it is worth noting that vitamin D receptor polymorphism also exerts a crucial influence on both vitamin D status and vitamin D metabolism[82,83].

We conducted comprehensive subgroup and sensitivity analyses to thoroughly investigate the sources of heterogeneity, and our results remained robust even after adjusting for confounding factors or conducting additional sensitivity analyses. Based on these findings, it is imperative to consider implementing routine screening for vitamin D concentrations in individuals with diabetes, particularly those with DFUs. Furthermore, it is advisable to administer vitamin D supplementations to individuals exhibiting inadequate or deficient levels of this nutrient, particularly among elderly patients with long-standing diabetes and suboptimal glycemic control. Based on animal models, the latest research findings[84,85] support the involvement of vitamin D in wound healing, while there remains a debate regarding routine vitamin D supplementation in patients with DFUs. However, careful consideration must be given while interpreting findings derived from subgroup analysis and meta-regression utilizing average indicators due to the absence of individual-level data. For instance, it should be noted that studies involving participants with a mean age of 50 years or younger may also include individuals aged over 50 years in both DFUs and non-DFUs groups. Conversely, a similar situation could arise in subgroups with a mean age exceeding 50 years. Therefore, caution should be exercised when interpreting the findings derived from subgroup analysis and meta-regression.

However, it is crucial to meticulously consider several limitations of the present study. Firstly, the analysis was solely conducted on trial-level data, without access to individual-level data. This limitation also applies to the subgroup analysis. For example, our subgroup analysis relied on mean HbA1c values in order to ascertain whether the disparity in vitamin D concentrations is confined to subjects with poor glycemic control. However, the inclusion of individual-level data would enhance its reliability and strengthen the findings. Secondly, due to limited available data, a comprehensive investigation into sources of heterogeneity was not possible. Consequently, potential confounding factors such as ulcers severity, dietary habits, and other variables could not be adequately accounted for. It is important to note that these included studies encompassed both outpatients and inpatients, while those with inpatients may introduce bias towards more severe ulcers. Thirdly, there was a lack of consistency in the methodology employed for assessing serum vitamin D concentrations across the studies included, as several studies omitted reporting this crucial information. Additionally, there was a substantial variation in absolute values of vitamin D concentrations among the included studies. Fourthly, the utilization of case–control and cross-sectional designs instead of RCTs hindered the establishment of causal relationship. Moreover, the imprecise temporal sequence between the occurrence of DFUs and assessment of vitamin D status also limited the ability to establish causality. Therefore, it is crucial to interpret these findings with caution.

Conclusions

The findings of this meta-analysis suggest that patients with DFUs exhibit lower serum vitamin D concentrations compared to those without DFUs, particularly among the elderly population with long-standing diabetes and poor glycemic control. Vitamin D deficiency and insufficiency may potentially contribute to the increased susceptibility to developing DFUs. However, the causal relationship between vitamin D status and DFUs remains unclear. Given the underlying supporting mechanisms, this clinical issue holds significant practical implications. Therefore, if maintaining adequate vitamin D concentrations proves beneficial in preventing DFUs, vitamin D supplementation could serve as a safe, cost-effective, and widely accessible potential therapeutic approach for individuals with DFUs. Nevertheless, further investigation is warranted to establish a definitive causal association between vitamin D status and the development of DFUs.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

XR and WT devised the research plan, demonstrating their expertise in study design. WT and DC conducted a comprehensive review of relevant studies, ensuring a thorough examination of existing literature, and meticulously extracted the data with great attention to detail. GL and WT performed rigorous data analysis using advanced statistical methods, enhancing the reliability of the findings. The manuscript was skillfully composed by WT, showcasing her proficiency in scientific writing. LC, SS, CW and YG diligently revised the manuscript

to improve its clarity and coherence. All authors have thoroughly reviewed and given their approval to the final version of this scholarly work.

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Declarations

Competing interests
The authors declare no competing interests.

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